32. One comment urged that this section contain a comparison analysis of human and animal pharmacokinetic data and the rationale for setting the specifications for the drug substance and drug product based upon the results of bioavailability studies.

FDA does not agree that the final rule should require a comparison of human and animal pharmacokinetic data. Animal pharmacokinetic data are generally most relevant during the investigational phases of drug development, where they permit the establishment of parameters for the safe use of the drug in human subjects. After human pharmacokinetic data are collected, however, they alone are usually adequate for review of an application. An applicant is free, however, to provide a comparison analysis of the animal and human data if the applicant believes it results in a clearer presentation. At the same time, the agency agrees with the suggestion for inclusion of the rationale for specifications and analytical methods for the drug substance and drug product needed to assure the bioavailability, and FDA has revised the final rule to add that requirement. The rationale for establishing specifications and analytical methods, with the data and information supporting the rationale, is needed to determine whether the proposed specifications or methods will assure the bioavailability of the drug substance or drug product.

33. One comment objected to the statement in the preamble that bioavailability data are needed to assure batch-to-batch consistency and to reevaluate product reformulations or changes in manufacturing processes. The comment argued instead that simpler methods, such as in vitro dissolution, are adequate.

The ability of in vitro dissolution data to determine the bioavailability of a batch of a drug product depends, in FDA's view, on whether the data can be correlated with in vivo data. Generally in vivo bioavailability data and in vitro dissolution data are examined and, if possible, in vitro dissolution methods and specifications are set for the product. Subsequent batch-to-batch consistency is assured by testing each batch by the in vitro method and evaluating the results against the in vitro specifications. Thus, bioavailability data are often needed to establish the simpler in vitro tests.

34. One comment urged that the summarizing discussion and analysis be clearly required at the beginning of the pharmacokinetics and bioavailability section because it brings together information not necessarily present in each of the bioavailability and bioequivalence studies. This comment also suggested that this section should require that the analytical and statistical methods used in each study be described in the report of the study, and not grouped together in a separate section as the proposal suggests. Moreover, the comment believed that each study should be evaluated as an entity because that is the way reports of studies are prepared. The comment asserted that breaking reports in this section apart is likely to lead to errors.

FDA believes this comment misunderstood the proposal. The regulation is intended to describe in general terms the kinds of data and information that are required to appear in this section and the applicant is free to present it in the format that provides the clearest presentation, which may include either an opening or closing summary. Because FDA agrees that, in most instances, the analytical and statistical methods used in each study should be described in the study report, the agency has revised the regulation to suggest that use of that format is usually preferable. Again, however, FDA believes the applicant should use a format that provides the clearest presentation and permits the most efficient review.

*Clinical Data Section -- General (§ 314.50(d)(5))*

35. One comment objected to the requirement that the results of each human clinical pharmacology study be compared with the animal pharmacology and toxicology data. The comment explained that most toxicology studies use doses higher than those used in human studies and often for longer periods of time, and that animal pharmacology studies may include disease states in animals not present in clinical studies. Thus, according to this comment, applicants should only be required to compare the results of clinical pharmacology studies with the "major findings" of animal pharmacology and toxicology studies. Another comment urged that this requirement be limited to information related to the intended use of the drug under its proposed labeling and to possible side effects to ensure that the applicant and the agency do not become sidetracked on issues related to potential new indications for the drug.

The agency does not agree that it is necessary to limit the comparison between clinical pharmacology data and animal data, as suggested by the comment. The proposal's call for "a brief comparison of the results of human [pharmacology] studies with the animal pharmacology and toxicology data" is intended to require an examination of the clues to potential usefulness or toxicology in humans provided by animal data. With respect to the second comment, virtually all of the pharmacologic properties of a drug are pertinent to the intended use of the drug, even those properties that are not

the ones leading to the drug's intended use. The human results should thus be compared to all pertinent animal observations. If no human observations concerning a particular property exist, of course, no comparison can be made.

36. Noting that a controlled clinical study on a drug may not be relevant to the indications proposed in the application, one comment suggested that the final rule should only require a description and analysis of each controlled clinical study pertinent to the proposed indications for the drug and that other controlled studies should be included in the general description of other data or information relevant to an evaluation of the safety and effectiveness of the drug. This comment also suggested that the regulations require only that the applicant describe, and not analyze, data from studies that are not controlled.

FDA has revised the final rule to require description and analyses of controlled clinical studies pertinent to a proposed use of the drug. The agency notes, however, that § 314.50(d)(5)(iv) still calls for "a description and analysis of any other data or information relevant to an evaluation of the safety * * * of the drug product" not a "general description" as implied by the comment, and does require some analysis of controlled studies not pertinent to the proposed uses of the drug. FDA continues to believe that the usefulness of sources of data, such as clinical trials of drug uses other than those proposed, depends on a reasonably detailed description and analysis of the safety of those trials. The agency notes, however, that the proposal did not require analyses of uncontrolled studies, but only a description of them, which accords with the comment's suggestion. Finally, FDA has revised the final rule to include a requirement for a brief description of pertinent studies that have been discontinued or are ongoing.

37. One comment objected to a requirement for safety data from epidemiological studies of related drugs, believing that the requirement is vague and potentially subject to an overbroad application.

The agency does not believe that information about related drugs, such as epidemiologic data, can be ignored in evaluating a new drug. An applicant developing a new member of an already established drug class usually is, and should be, conscious of the experience with other members of the class. Such information may be relevant to labeling and may help focus the evaluation of the data submitted. FDA does not believe that the requirement will be applied unreasonably.

38. On its own initiative, the agency has made two additional changes in the final rule. First, FDA has added an explicit requirement for the applicant to synthesize, in an integrated summary, the data which it believes provide substantial evidence of effectiveness of the drug for its proposed uses (§ 314.50(d)(5)(v)). FDA believes that this requirement was implicit in the proposed requirements for an overall summary to help the agency prepare the SBA document, but has determined that a specifically focused discussion in the clinical section will significantly facilitate review. Second, the final rule also requires an applicant to explain briefly why a study is not considered adequate and well-controlled. This will enable the agency reviewers to determine what conclusions can be validly drawn from those studies.

*Safety Update Reports (§ 314.50(d)(5)(vi)(b))*

39. FDA received several comments on the proposed "safety update reports," which are designed to advise FDA of new safety information that becomes available while the application is being reviewed by the agency. The proposal would have required such reports at 4-month intervals and upon receipt of an approvable letter. Although most of the comments addressing this issue favored the concept of safety update reports, concerns were raised that the reporting intervals were too frequent and that the data being requested were more than were necessary. Concerns were also raised that, if not properly limited, the requirement for safety update reports could delay the approval process by creating an ongoing need to review more data.

FDA believes that the basis for the proposed safety update reports, which is to ensure that drug approvals are based on the most up-to-date safety information available, is sound. FDA has, however, revised the final rule to ensure that reporting obligations are no greater than are needed, so that the requirement does not unduly delay approvals.

First, FDA has defined more precisely the type of information that needs to be reported. Whereas the proposal simply said "new safety information," the final rule specifies "new safety information * * * that may reasonably be expected to affect the statement of contraindications, warnings, precautions, and adverse reactions contained in the draft labeling." Thus, under the final rule, the only information that must be submitted in a safety update report is safety information that is different from that previously submitted and that may warrant revision in the draft labeling. It should be emphasized that (1) "new" information includes both adverse effects that were never seen before and a material change in the frequency or severity of effects that were recognized previously; and (2) case report forms for patients who die or who leave a study prematurely because of an adverse event are always required (unless the requirement is

waived). Thus, for example, new safety information that suggests that an adverse effect occurs at a higher rate than previously thought would be required because it might change a precaution to a warning in the labeling.

Second, FDA has revised the reporting intervals so that safety update reports will be required (1) 4 months after the initial submission; (2) following receipt of an approval letter: and (3) at other times as requested by FDA. The first safety update report is important because it is designed to let reviewers know if any major new data are available that could affect their recommendations regarding approval of the drug. This first report covers a much longer period than 4 months because it also covers the time period between the "data lock point" and submission of the application, during which time the applicant is preparing the application for submission to the agency. The report following an approvable letter is intended to provide the agency with the most current information available immediately before approval. Moreover, it parallels the normal submission of final printed labeling so that FDA reviewers can be assured that the labeling is up-to-date. In addition, FDA may request safety update reports at other times, such as before an advisory committee meeting or before an approval letter where an unusual amount of time may have passed since issuance of the approvable letter. This may also include the situation where the agency intends to issue an approval (instead of an approvable) letter based on draft labeling, and a special request for a final safety update report will prevent undue delay. Thus, by replacing the "every 4 months" requirement with discretionary requests by the agency, the regulations allow applicants to submit interim reports only when the agency believes they are necessary for review and approval of the application.

FDA does not believe this policy will delay the approval process. As noted above, the reports themselves are tied to information pertinent to labeling, and will be in a familiar format, permitting prompt review. Moreover, FDA expects that major changes in safety information will not be common. If an applicant, however, does obtain new safety information that is so significant that it could affect the overall risk/benefit determination of the drug for one or more indications, a further extension of the review process will inevitably be necessary.

The guideline on the clinical section of the application will describe the format of both original safety reports and updates.

*Samples and Labeling (§ 314.50(e))*

40. Several comments suggested that requiring four samples is excessive and that FDA should request only the actual amount needed.

FDA's experience is that four samples are needed to perform necessary testing. One sample is tested by each of two FDA laboratories, for purposes of replication, and the two remaining samples are held as reserve samples for each of those laboratories in the event that additional testing is necessary. In addition, the final rule represents a significant reduction from past practice in the amount of samples applicants must submit to support approval of an application. Samples are no longer required, for example, of the finished dosage forms used in the clinical investigations, nor of the new drug substance used in manufacturing those dosage forms. FDA has revised the final rule to increase from two to three copies of the analytical methods and related descriptive information FDA needs to test the samples. One copy is needed for each of the FDA laboratories assigned to test the samples and a third copy is needed for the agency's headquarters files.

41. One comment urged that samples be required earlier in the review process, specifically either at the time the application is submitted or when the application is filed. This suggestion was aimed at ensuring that necessary testing is completed on time and does not delay approval of the application.

FDA disagrees with this comment. Under the final rule, the FDA reviewer will contact the applicant to request samples and provide laboratory assignments after a preliminary review of the analytical procedures indicates that the procedures are satisfactory. The date of filing is not appropriate because the review necessary to determine whether an application is complete and can be filed is not as detailed as the review needed to determine whether analytical procedures are satisfactory. The procedure in the final rule will prevent the premature submission of samples and will ensure that methods validation testing is not conducted on outdated samples. The procedure should not, however, delay the review process so long as applicants make every effort to provide the samples when requested. Moreover, as noted above, it is FDA's policy not to delay approval of a drug solely because methods validation has not been completed.

42. Several comments questioned whether, by combining requirements for samples and labeling, the proposal implied that labeling should be submitted only upon request. Another comment asked FDA to clarify what it means by "related descriptive information" and noted that the proposal would not have required submission of results of the applicant's tests on samples.

FDA has revised the final rule to state that copies of the product's label and labeling should be submitted with the application, and not only upon request. The final rule also states that "related descriptive information" includes a list describing each submitted sample; a list of proposed regulatory specifications; a detailed description of the methods of analysis; supporting data for accuracy, specificity, precision, and ruggedness; and complete results of the applicant's tests on each sample.

43. One comment urged that the current exclusion for sterility and pyrogen testing samples, which was not contained in the proposal, be retained.

Although FDA agrees that sterility and pyrogen testing samples are often unnecessary, particularly if the testing procedures are ones generally recognized as valid (for example, procedures established in the official compendia), new testing procedures may be developed (for example, the limulus amebocyte lysate test for pyrogens) that warrant FDA review. Accordingly, the final rule requires their submission, but FDA will consider waiver requests on a case-by-case basis.

44. One comment suggested that the final rule should follow the current practice and require the submission of only one finished market package.

FDA has revised the final rule to eliminate the suggestion that four samples of the finished market package are required. Samples of the finished market package are required to be submitted only if FDA requests them and, although the agency generally requests only one sample, two are sometimes needed. The final rule provides this flexibility.

*Case Report Forms and Tabulations (§ 314.50(f))*

45. FDA received many comments on the proposed submission of individual clinical data using a combination of case report forms and tabulations. A number of the comments misunderstood the meaning of the terms used and their interrelationship. For example, some comments erroneously equated "case report forms" with "raw data," while other comments mistakenly understood "tabulations" to be the same as "summaries." Before addressing the specific comments, therefore, these terms need to be clarified in the context of the current regulations and the NDA Rewrite proposal.

a. *Raw data.* The "raw data" from a clinical study are the clinical investigator's own records of the individual patients. These records include the patient charts, hospital records, x-rays or other laboratory test results, and notes of the attending physician. These raw data, even under current regulations, are not routinely submitted to FDA as part of a new drug application, but instead remain in the files of the clinical investigator or hospital for FDA audit, if necessary.

b. *Case report forms.* These are the documents that the clinical investigator sends to the drug sponsor that list all the data collected on each individual patient. There is 1 case report for every patient in each study, and case reports typically vary from 5 to 50 pages in length. Under current regulations, all case reports must be submitted to FDA as part of a marketing application. Because such applications frequently contain data on from 1,000 to 3,000 patients, case reports consume a great many volumes in a typical application.

c. *Tabulations.* These are tabular listings of the individual patient data, as taken from the case report forms. The tabulations are prepared by the drug sponsor, usually using an automated data processing system. By using tabulations, the results from a study of a given medical parameter (e.g., blood pressures for an anti-hypertensive drug) can be presented on one or two pages. These tabulations contain the very same numbers as the case report forms on which they are based, and the data are clearly identified by individual patient. Thus, tabulations are ordinarily a more concise and efficient representation of the data contained on the case report forms.

d. *Summaries.* These are usually narrative documents, often interwoven with summary tables and graphic presentations of data, that present the results of a study, using the analyses deemed appropriate. Summaries are the most common means of communication in science, and most scientific journal articles are summaries in this sense, as are the descriptions and analysis called for in the clinical section of the application. Summaries, however, are by their nature interpretive documents that select certain data as being important. Thus, summaries reflect a point of view about what the data mean, and the point of view and data selections are always shaped by the judgment of the writer.

e. *Current requirements.* Current regulations require the routine submission of all case report forms. Use of tabulations is voluntary with the applicant. Recognizing the inherent difficulty of relying on the case report forms themselves to find individual data elements, it is extremely common for applicants to submit tabulations voluntarily in some form

to make the review of the data more efficient. Applicants use such tabulations in their own analyses, subjecting them to a variety of statistical procedures to develop analyses and summary tables presented for each study report.

f. *The proposal.* Based on the agency's positive experience with tabulations, FDA proposed to substitute tabulations for case report forms as the primary focus of the data review. Under the proposal, some case report forms would still be required routinely (i.e., for patients who died during or who dropped out of a clinical study due to an adverse event) because these cases are the ones most likely to reveal significant safety problems and demand individual case-by-case review. Also under the proposal, FDA would have access to additional case reports whenever a legitimate need existed. Thus, the intent of the proposal was to focus the agency's review on a more concise and efficient mode of data presentation, while still providing the agency with complete individual patient data. The proposal also contained a requirement for summaries, but only to complement and integrate the individual patient data contained in the case reports and tabulations.

46. FDA received a considerable number of comments on this provision, concerning primarily the concept of how data should be submitted (i.e., summaries versus tabulations versus case report forms). Comments on both these subjects covered a wide spectrum. Several comments argued that all case report forms should be routinely required, on the ground that FDA needed this "raw data" to conduct a full scientific review. In contrast, other comments suggested that even the review of tabulations would be more time consuming than necessary, and that FDA should instead rely on summaries alone.

FDA believes that the proposal to require data submission through a combination of summaries, tabulations, and case report forms allows a scientific review that is both thorough and efficient. FDA believes that, for many purposes, tabulations can provide adequate information for review because these tabulations will be required to contain the same individual patient data listed on the case report forms. As described above, even case report forms are not actually "raw data" (but instead constitute individual patient data as transposed by the clinical investigator from the doctor's charts), so concerns raised about the agency no longer requiring "raw data" are misplaced.

FDA also disagrees with the suggestion that it rely on summaries alone, without a routine submission of individual patient data (either as case report forms or tabulations). As noted above, summaries are, by their very nature, interpretive documents. Although summaries are extremely useful in reviewing applications, FDA believes they need to be complemented by the underlying data (either in tabulations or case report forms) for the agency to be able to conduct a thoroughly independent and objective review.

In response to these comments, however, FDA has reevaluated the proper mix of tabulations and case report forms that should be required. Although FDA believes that tabulations will be extremely useful in promoting a more efficient review process, the agency also recognizes that there are some inherent limitations on the use of tabulations and that, in certain instances, direct reference to case reports will be necessary. Theses may include, for example, instances where important narrative or other information on the case report form is not amenable to tabular presentation, or where case reports are desired to spot check the accuracy of the tabulations.

Accordingly, in order for the agency to conduct a scientific review that is both thorough and timely, a complete set of case report forms will ordinarily be needed for the most critical studies. In order to choose these appropriately, and at a time when they can be provided without causing delay, FDA reviewers will designate, approximately 30 days after receipt of an application, the critical studies for which case reports will be requested. These studies will ordinarily also be the ones utilized by the Division of Scientific Investigations in conducting its on-site data audits, and that division will make use of the same case reports, whenever possible, in order to eliminate the need for duplicate submissions.

FDA believes this policy is consistent with its overall goal of improving the efficiency of the drug review process. By relying more heavily on summaries and tabulations, FDA's initial review will be focused onto a more concise form of data presentation. This initial review, however, may trigger the need to review certain patient histories in more detail, especially those from the most critical studies, and case reports provide the basis for that more detailed review. Requests for full case reports from certain critical studies does not necessarily imply the need for a case-by-case review of every patient; instead, such requests are intended to ensure that FDA reviewers can make reference to, when needed, case report forms for those patients requiring further review. By making such requests approximately 30 days into the review process, delay is unlikely to occur.

Even with this modification, FDA estimates that there will be an average reduction of about 75 percent in the number of case reports that are routinely requested, when compared to the current requirement of full submission. As reviewers become more comfortable with tabulations, and applicants become more skillful in making them usable, it is

possible that requests for case reports will decrease. The regulation itself is general in nature so as to accommodate both the present expectation and any future changes.

47. Several comments that opposed the substitution of tabulations for most case report forms were concerned that this change could enhance the possibility that FDA would receive inaccurate data.

FDA does not believe that this change will decrease the accuracy of the data received or undermine the agency's ability to assure data accuracy. First, FDA's Division of Scientific Investigations routinely conducts a data audit on two or more critical studies in each marketing application. Such data audits compare the data on case report forms to the raw data retained by the clinical investigators. The policy of conducting these audits will continue. In addition, as noted above, medical reviewers may need to spot check the accuracy of tabulations for the most critical studies by comparing them to the data in the case report forms, and FDA can request the submission of case reports for that purpose.

48. FDA received a number of comments on the proposed standard that additional case reports could be obtained whenever a "legitimate need" existed to conduct an adequate review of the application. Comments generally believed that this provision was vague. Many interpreted it as an attempt to discourage requests for additional case report forms. Several comments, on the other hand, were concerned that the provision would lead to excessive requests and urged that the final rule contain explicit criteria for justifying request, and that requests should be made in writing with a supporting rationale.

FDA had modified this provision in the final rule to reflect the agency's central concern -- namely, to permit the agency access to case report forms when it believes that they are needed to conduct a proper review of the application. The agency did not intend the phrase "legitimate need" to imply a barrier, and the final rule has been modified to contain more neutral language. FDA recognizes the concern expressed by several comments that some reviewers may be prone to request more case reports than the applicant believes are necessary. Although there will inveitably be differences among reviewers, FDA believes that assuring the reasonableness of requests for case report forms is the responsibility of FDA management. To strike what FDA believes is the appropriate balance between these competing interests, the final rule provides that all requests for additional case reports (other than those required to be routinely submitted) must be approved by the director of the division responsible for reviewing the application. Any applicant that feels it is being asked for an excessive number of case reports may raise the matter directly with the releveant division director or with the ombudsman.

FDA notes that the need for additional case reports will likely vary according to the type of drug under review. For example, case reports appear to contribute significantly less to the efficacy review of an anti-hypertensive drug because blood pressures can quite adequately be complied in a tabulation, patient dropouts are usually few, and most patients entered into a trial are analyzed. Conversely, FDA believes that case reports may be critical to the review of controlled studies for an antibiotic drug. This is because the efficacy determination for an antibiotic turns largely on which patients were included and which were excluded from the study analysis, and the reasons for inclusion or exclusion often involve close judgments that cannot readily be shown in a tabulation. FDA will advise applicants, either in guidelines or in "pre-NDA" conferences, of particular case report needs for particular drug classes.

49. Several comments addressed the time aspect involved in FDA requesting additional case report forms or tabulations. One comment was concerned that the proposal might actually delay the review process, because reviewers would have to wait for the submission of additional case report forms. Another comment suggested that the 30 days for the submission of case report forms, as provided in the proposal, may not be adequate. A third comment suggested that, if additional case reports or tabulations are submitted more than 30 days following an FDA request, any extension to the review period should be limited to the number of days the submission was late.

FDA does not believe that this requirement will cause delay in the review process. Case report forms are still required to be maintained by drug sponsors, and the time needed to respond to requests should be relatively short. Moreover, applicants, who themselves seek an expeditious review, have an incentive to respond to such requests quickly. Finally, as noted above, the agency's policy of identifying needed case report forms early in the review process should also help reduce delay. When applicants do take more than 30 days to respond, the agency considers it reasonable to extend the review period in accordance with § 314.60. The length of such extension will involve not only the time taken to respond, but also other factors, such as the stage of the review process and the reasons for the request. For example, case reports requested to investigate data discrepancies may require a longer extension than requests for case reports to provide information not contained in the tabulations.

50. Several comments urged that FDA require the routine submission of case report forms for deaths and dropouts only for patients who receive the investigational drug, and that case reports for patients on placebo or a reference drug not be included. In addition, one comment asked whether the term "adverse event" in this section of the proposal would include a patient who dropped out of the study because of a "lack of expected pharmacological effect."

FDA believes that case report forms for deaths and dropouts are particularly useful for determining safety problems with a drug. In determining whether these events were drug-related, FDA's evaluation necessarily includes comparing safety problems for patients who took the test drug with patients in the control group who also died or dropped out of the study. Thus, the agency believes that this provision of the final rule should not distinguish between patients in a study on the basis of whether they actually received the investigational drug, and the final rule has been so revised. The term adverse event in this context (as distinguished from its use in § 314.80 concerning postmarketing surveillance) does not include "lack of expected pharmacologic effect."

51. Several comments addressed the level of detail required in the tabulations. A number of comments objected to requiring "every datum" obtained on each patient so that FDA reviewers can reanalyze the data already analyzed by the applicant. These comments preferred tabulating data on categories of patients, which is the standard procedure used in submitting papers to scientific journals. Another comment took the opposite view and suggested that the tabulations include full listings of individual patient data. One comment simply asked that FDA clarify the level of detail needed.

As a general rule, FDA believes that individual patient information that is important enough to be recorded on a case report form would be pertinent to the agency's review of the drug's safety and effectiveness. As noted earlier, the tabulations are intended to present essentially the same information as the case reports, except in a more efficient form.

Nevertheless, the agency recognizes that not all individual patient information will be needed for the agency to conduct a proper review of the application. The regulation, for example, exempts from submission tabulated data on effectiveness derived from uncontrolled Phase 2 and Phase 3 studies. This is because the agency's effectiveness review relies upon adequate and controlled studies, as required by law.

The regulation further provides that the applicant may delete additional tabulations which the agency agrees, in advance, are not pertinent to a review of the drug's safety or effectiveness. Upon request, FDA will discuss with the applicant in a "pre-NDA" conference those tabulations that may be appropriate for such deletion. The regulation also provides that, barring unforeseen circumstances, tabulations agreed to be deleted at such a conference will not be requested during FDA's review.

*Other Information (§ 314.50(g))*

52. One comment suggested that applicants be permitted to submit English language abstracts that appear in original publications in foreign languages and that they be required to submit an English translation of the full publication only upon request.

The agency believes that it is not unreasonable to ask an applicant who relies upon an original literature publication in a foreign language to submit both the foreign publication and an English translation of it. Otherwise, FDA would not be able to review the full presentation. This is not a new requirement.

*Format of an Original Application (§ 314.50(h))*

53. Several comments addressed the provision whereby applicants could submit the archival copy of the application on microfiche. Comments generally suggested that limiting submissions to microfiche is too restrictive and that FDA should permit microfilm and other data storage forms. One comment suggested that roll microfilm is more economical and easier to make hard copies from than microfiche. Some comments stated that most applicants already submit copies of raw data on indexed microfilm to Canadian drug approval authorities, and that the same form should be acceptable in this country. One comment also suggested that case report forms should be permitted on microfiche or roll microfilm.

FDA has revised the final rule to provide that applicants may submit the relevant portion of an application on microfiche or, if FDA agrees, on another suitable microform system. This change would permit the use of new microform technologies while ensuring that the submission would be in a form usable by FDA. Although other currently available systems (such as indexed roll microfilm) have some advantages over other microform systems, they also have significant disadvantages when used under the circumstances of an FDA application review because of the difficulty in locat-

ing specific information even in well-indexed systems. Decisions on using alternative microform systems will be made on a case-by-case basis, as will decisions on whether a microform system may be used for case reports and tabulations.

*Abbreviated Applications (§ 314.55)*

Note. -- On September 24, 1984, the President signed into law the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417). A primary purpose of this law is to greatly expand the universe of drugs for which FDA will accept abbreviated applications. Pursuant to section 105(b) of the new law, on November 26, 1984, FDA began accepting such applications. Section 105(a) of the new legislation provides FDA with 1 year from the date of enactment to promulgate new implementing regulations. Section 105(b) further provides that, until such time as FDA has new implementing regulations in place, the currently existing regulations will be effective, absent a conflict with the new statute. Because the provisions in this final rule governing abbreviated applications merely restate, in slightly different form, the current regulations on this subject, FDA considers these provisions of the final rule to have the same effect under section 105 of the new law as do the current regulations governing abbreviated new drug applications.

54. One comment asked how the standard of "very closely related" in proposed § 314.56(c) for determining whether an abbreviated application is suitable differs from the standard of "identical, related, and similar drug products" in § 310.6 (21 CFR 310.6) for applying FDA's efficacy conclusions in the Drug Efficacy Study Implementation (DESI) project.

In the Federal Register on January 21, 1983 *(48 FR 2751),* FDA amended its new drug regulations to clarify its policy on when abbreviated new drug applications are suitable and will be accepted. That rule states that, when FDA finds that an abbreviated application is suitable for a drug product, the finding will apply only to drug products "identical" to the product that was the subject of the finding. At the same time, FDA established a petition procedure under which prospective applicants may ask FDA to determine whether an abbreviated application is suitable for similar or related products. Such decisions on suitability will be made on a case-by-case basis, and abbreviated applications will be accepted only if the safety and efficacy data on the first product are applicable to the product that is the subject of the petition. FDA has revised § 314.55 to conform to the text of that final rule.

In the preamble to the January 21, 1983 final rule, FDA addressed the relationship of this provision to the DESI policy contained in § 310.6. As stated in that preamble, a DESI finding of effectiveness for one drug product does not automatically apply to all similar or related products. Rather, "There will be * * * areas where the judgments of experts must determine the applicability of efficacy findings. The determination will be based on the chemical structure of the drug, recommended use, route of administration, its pharmacological properties and any other information available on the action or properties of the drug." *(48 FR 2751 at 2753.)* It is through the petition procedure described in § 314.55 that this determination will be made.

*Application Development File*

55. FDA has removed from the final regulations the proposed provision on the application development file (proposed § 314.57). The provision would have established a mechanism for prospective applicants of abbreviated applications to obtain agency comments on their formulation data, dissolution data, bioequivalence protocols, and pilot studies before conducting bioequivalence tests. FDA has determined that a codified procedure is unnecessary because less formal procedures for providing guidance to potential applicants exist. For example, FDA provides applicant with guidance on developing bioavailability studies through guidelines, meetings between applicants and agency staff, and general correspondence. Moreover, many applicants now rely upon contract laboratories to conduct bioavailability studies, and these laboratories are generally familiar with the requirements for performing acceptable bioequivalence studies. The agency also believes that providing general prospective guidance on bioavailability studies, as opposed to application-specific review, will consume significantly less agency resources while providing adequate guidance to potential applicant.

*Amendments to an Unapproved Application (§ 314.60)*

56. Several comments asked that FDA inform an applicant if the agency considers a submission to be a major amendment and the approximate amount of time the division needs to review it. Some of these comments urged FDA to reply within 30 days after the agency receives the amendment. Other comments urged that the final rule clarify that the

maximum extension will be 180 days. One comment suggested that, if an amendment is made in response to an agency request, FDA should inform the applicant within 30 days of whether the response was adequate.

As stated in the proposal, the director of the reviewing division will inform an applicant that submits a major amendment if an extension is needed. The agency has clarified the final rule to state explicitly that the division director will also inform the applicant of the amount of time the division needs to review the amendment. The agency will strive to make such notifications as timely as possible. FDA has added a statement to the final rule to clarify that the maximum extension of the review period will be 180 days. Finally, FDA may notify the applicant of particular deficiencies found in the amendment and request further clarification or, depending upon the deficiency, may respond to it in an action letter. In this respect, agency comments on an amendment will be handled in the same way as on any other part of the application.

*Supplements and Other Changes to an Approved Application (§ 314.70)*

57. FDA views the requirements under which applicants can make manufacturing and controls changes in their approved applications as an area in which it can significantly reduce regulatory burdens on the drug industry without compromising public health protection. Currently, nearly all changes in the conditions originally approved in the application are subject to prior FDA approval in a supplemental application, with the few exceptions listed in the regulations. In the same manner suggested by the proposal, the final rule changes this scheme significantly by reducing the number of changes that require supplements and listing those changes (instead of the exceptions) in the regulations. Thus, the final rule retains the three proposed regulatory categories: (1) prior approval, for those changes in marketed drugs which could affect FDA's previous conclusions about the safety and effectiveness of the drug; (2) changes requiring supplements concurrent with the change but on which FDA prior approval is not necessary; and (3) annual reports for changes that do not fall into one of those two categories. The final rule, like the proposal, specifically lists the kinds of changes falling into the first two categories. The final rule also lists examples of changes that can be described in the annual report, but the list is not intended to be exhaustive because the annual report is the residual category.

In the proposed rule, FDA identified several areas where it believed applicants could make changes in their approved applications under less restrictive conditions than currently required. Since then, FDA has conducted an exhaustive examination of its current practices with respect to supplements and has determined that, although significant improvements can be made in this area, for the reasons stated below, not all of the proposed changes have been implemented. As a result, FDA has realigned the specific types of changes among the three categories and is returning several kinds of changes to the prior approval category that, under the proposal, could have been reported to FDA following implementation. At the same time, however, FDA will permit annual reporting of some changes that, under the proposal, would have required prior approval. Under the final rule, FDA estimates that there will be a reduction in approximately 20 percent of manufacturing and controls supplements that now require prior approval, all in areas not likely to affect the safety or effectiveness of the finished drug product. Although FDA proposed to permit the following changes without prior approval, the agency is retaining in the final rule the current prior approval requirements for changing a contract laboratory or labeler, establishing new procedures for reprocessing a batch of a drug product that fails to meet specifications, changing the synthesis of a drug substance, and changing the facility or establishment for manufacturing the drug substance in certain instances. FDA has concluded that prior approval of these changes is needed because they can significantly affect existing agency safety and effectiveness conclusions about a product.

First, FDA has concluded that it should preapprove the ability of a contract laboratory or labeler to comply with CGMP regulations, for such compliance relates directly to the ability of the laboratory or labeler to produce a drug of acceptable quality and/or properly labeled. Second, with respect to the prior approval requirement for reprocessing a batch that fails to meet specifications, many critical factors affect the acceptability of reprocessed batches; for example, the reason for the original batch failure, the storage conditions of the original batch, the tests performed on the reprocessed batch, and the stability of the reprocessed batch. Prior approval of reprocessing procedures will best ensure that rejected batches are not blended with accepted batches, that stability data are used to support recovery or reprocessing operations, and that original control tests are adequate to monitor the reprocessed batch.

Third, prior approval to change the synthesis of the drug substance is needed to assure the safety and effectiveness of the finished product, as is the use of a new facility to manufacture it in certain instances. A change in the synthesis and the many changes in equipment and procedures that occur with a change in manufacturing facilities may significantly affect the finished product. For example, such a change may affect the particle size, crystalline form, stability, or dosage form dissolution of the drug and, thus, affect the bioavailability of the finished product. The method of synthesis

of a drug substance is also linked to specifications needed to monitor its strength and purity. Prior approval will ensure that applicants who make a change in synthesis reexamine the adequacy of specifications in light of that change. A product from a different route of synthesis may yield a different purity profile and may require in vivo testing because the limits for specific impurities are normally developed with reference to their toxicity and pharmacological properties. Finally, impurities may also affect the stability of the finished product. In sum, given the significance these changes may have on product safety and integrity, FDA belives it necessary to maintain premarket approval with respect to them.

With respect to changing the facility or establishment that manufactures the drug substance, prior approval will be required where: (1) the manufacturing process in the new facility or establishment differs materially from that in the former facility or establishment, or (2) the new facility or establishment has not received a satisfactory current good manufacturing practice (CGMP) inspection within the previous 2 years covering that manufacturing process. However, the final rule also provides that an applicant may change the facility or establishment that manufactures the drug substance, without obtaining prior FDA approval, if: (1) The manufacturing process in the new facility or establishment does not differ materially from that in the former facility or establishment, and (2) the new facility or establishment has received a satisfactory CGMP inspection within the previous 2 years covering that manufacturing process. If those two criteria are met, the applicant may implement the change concurrent with submission to FDA of a supplement. In that instance, the supplement is to be plainly marked, "Special Supplement -- Changes Being Effected."

FDA has also identified certain changes, in addition to those proposed, that may be reported to FDA on an annual basis rather than in a supplement. These include certain changes in the container and closure system for the drug product, and the addition or deletion of alternate analytical methods. These changes are described more fully below in response to comments on the proposal.

Finally, FDA has revised the final rule to provide a mechanism for applicants to obtain expedited review of supplements where special considerations exist. FDA generally reviews supplements subject to prior approval in the order in which they are received, taking into account other review priorities such as investigational new drug applications and applications for important new drugs. A longstanding and understandable concern of applicants is the cost of waiting for FDA to review and approve these supplements, particularly when extraordinary circumstances require a change in the conditions of approval; for example, when an unexpected event forces an applicant to use a different facility to continue manufacturing a product, or a technological breakthrough would greatly reduce costs. The agency has informally recognized the need to expedite such supplements, but believes that the regulations should specifically recognize this practice. Secondly, the agency has revised the final rule to permit applicants to request expedited review of a supplement for a change that requires prior approval. The agency emphasizes that expedited review is available only under extraordinary circumstances, for either public health or economic reasons, and is subject to the agency's discretion and available resources.

This section, like most of the final rule, will become effective May 23, 1985. If an applicant has submitted to FDA supplements for manufacturing and controls changes that do not require a supplement under the final rule, and those supplements have not yet been reviewed by FDA, the applicant should notify FDA in writing that it is withdrawing those supplements. Upon such notification to FDA, the applicant may proceed to implement those changes as permitted by the final rule.

58. Several consumer comments urged FDA to require prior approval of supplements for every change in an approved application to ensure the safety of the change.

FDA does not agree that prior approval of supplements for all changes in approved applications is necessary. For example, the deletion of an ingredient intended only to affect the color of the drug product is unlikely to affect safety or effectiveness. This is the type of change that, under the final rule, can be implemented by the applicant and submitted to FDA as part of the annual report. FDA believes its combination of prior approval requirements, requirements for supplements not requiring prior approval, and annual reporting requirements focus FDA's resources and attention on those issues that must be monitored closely and properly tailor the time of the reporting to the nature of the change.

59. Several industry comments stated that FDA's proposed reductions in its supplemental application requirements represent a major improvement over current practices. FDA received several comments, however, suggesting that, even with the proposed changes, the regulation of supplements would still be too restrictive. For example, several comments noted that the categories of changes are stated generally and might apply to many changes for which prior approval of a supplement should not be required. Another comment observed that, although the preamble suggested it would be unnecessary to explain batch control numbers in an original application, changes in the batch numbering system would be

required in an annual report. Finally, one comment suggested that the agency should permit a single supplement to cover all similar and related products; for example, a packaging change that may affect as many as 100 products should require only a single supplement.

FDA does not agree that the categories of changes are stated too generally. It must be remembered that applicants are to inform FDA about only those changes that affect the information previously submitted in the application. Thus, the application itself is a guide to the kinds of information for which, if changed, the applicant must submit a supplement. Moreover, as described more fully in the proposal, FDA will no longer require an original application to contain information about manufacturing practices that FDA monitors under its current good manufacturing practice (CGMP) regulations, a regulatory change that will also eliminate the need to submit supplements that would require prior approval under current regulations. Because batch control numbers fall under the CGMP regulations, an explanation of batch control numbers is not required in either the original application or the annual report.

Finally, the agency does not agree that a single supplement would be adequate to cover a change affecting similar and related products. Eliminating multiple supplements in favor of a single supplement would not affect the review time and speed of approval because FDA now combines those supplements and performs a single review if the applicant adequately notes the relationship of multiple submissions. Moreover, except for the submission of a supplemental application form for each application, the applicant may now make a single submission of the technical data and information necessary for the agency to review the change. Individual application forms are needed, however, because they are the mechanism by which the change is noted in each application. When approved, the supplement is placed in the application and becomes a part of the permanent record. The submission of a single supplement to cover multiple applications would impose an added burden on FDA to document the changes and is more likely than the current system to result in a failure to include documentation of the change in each application.

60. One comment asked whether changes in the manufacturing site of the drug substance require prior approval. Another comment objected that use of a facility for packaging a drug product should not require prior approval if the container and closure system and quality control procedures are unchanged, and the facility has undergone a recent CGMP inspection. Moreover, according to this comment, changes in the manufacturing site or the manufacturer of a drug product should not require prior approval if the method of manufacture and specifications of the ingredients are the same as those identified in the application and the drug product meets all specifications in the application.

FDA is obligated to see that approved new drugs are manufactured under circumstances that ensure that the marketed drug does not differ from the drug approved by FDA and, thus, that the agency's conclusions about safety and effectiveness apply to it. To accomplish these objectives, the agency must continually monitor the applicant's manufacturing and control operations, including packaging operations, to determine the applicant's ability to produce a product of acceptable quality. This includes prior approval of facilities for the manufacture of the drug substance and drug product and for packaging the product. Compliance with product specifications is important, but it cannot supplant the review process. The use of a new facility to manufacture a drug substance or drug product, or to package the product, invariably involves changes in procedures that may affect the agency's conclusions about the safety and effectiveness of the product. FDA encourages manufacturers to advise it early about plans to begin manufacturing or packaging operations in a new facility. When that is done, the agency and the applicant can work together to ensure that the requirement for prior approval of the supplemental application does not delay an applicant's use of the facility. Moreover, as described in paragraph 57 above and § 314.70(c)(3) of the final rule, prior FDA approval is not required when the applicant uses a new facility or establishment to manufacture a drug substance if certain criteria are met. Finally, FDA believes that the comment's confidence in the use of specifications to ensure product quality is too great. Quality is built into a product through the method of manufacture and in-process controls; end product testing is not viewed by FDA as a substitute for adequate control of the manufacturing process.

61. One comment noted that FDA's list of changes that would require prior approval of a supplement includes changes that can now be made at the time a supplement is submitted, and that FDA should continue to permit immediate implementation of all changes for which that practice now exists. Comments urged FDA to retain the provision in the current regulations that permits a change to be made when a supplement is submitted if the change gives increased assurance that the drug will have the characteristics of identity, strength, quality, and purity which it purports or is represented to possess. One comment suggested that FDA go one step further and permit a change without prior approval if the change provides the same level of assurance that the drug will possess its represented characteristics.

FDA did not intend either to require prior approval of any change for which prior approval is not now required or to change current practice with respect to those changes already listed in the regulations (21 CFR 314.8(d)) as giving in-

creased assurance that the drug will possess its represented characteristics. FDA has revised the final rule to retain the provision. The particular changes contained in the section can be made without prior approval because, by assuring to a greater degree that the drug will possess its represented characteristics, the change provides a public health benefit. A change that provides only the same level of assurance, however, does not provide such a benefit and, thus, the agency finds no basis for making the additional modification suggested by the comment.

62. One comment suggested that the proposal is more restrictive than current requirements in proposing that the "method of manufacture of the drug product, including changing or relaxing an in process control" must be approved by FDA before the change is made. Another comment objected to the phrase "the method of manufacture" because it is too broad and could apply to any change in the procedure for the manufacture of a drug product. One comment suggested that this requirement be revised to apply to changes that "make a significant change to the method of manufacture of the drug product, including changing or relaxing an in process control; for this section a significant change in method of manufacture should be defined as a change resulting in altered product specifications or altered in process controls."

As discussed above, a change in the method of manufacture should be made in the context of the original method of manufacture described in the application and approved by the agency. Moreover, the final rule omits the current requirements under which changes in manufacturing practices covered by FDA's CGMP regulations must be described in a supplement. This change already eliminates the need to seek prior approval for the kinds of changes in the method of manufacture that FDA believes are not significant.

63. One comment suggested that the requirement for prior approval of a new regulatory analytical method is inconsistent with the preamble statement that changes in analytical methods for the drug substance may be made and reported in the next annual report unless there is also a change in synthesis. An applicant suggested that a change in an analytical method should be allowed without prior approval when results are comparable to the approved method. Another comment urged FDA to permit the substitution of a less discriminating analytical method with a more stringent method without prior approval to reward innovation, reduce costs, and introduce benefit from technological advances. Several comments suggested that the agency should permit without prior approval a change in the container and closure system if the applicant demonstrates stability equivalence with the approved container and closure system under an approved stability protocol or where there is no significant alteration in the material of the components.

FDA notes that the comment is correct about the inconsistency in references to changes in analytical methods for drug substances. The preamble statement was incorrect; a change in a regulatory analytical method for a drug substance requires prior FDA approval because it is the method FDA relies upon to determine whether the product meets legal requirements. An applicant may, however, tighten the limits on a specification, or add a new specification without prior FDA approval, if the change is described in the next annual report. FDA is also persuaded that prior approval is unnecessary when adding or deleting an alternate analytical method because FDA will continue to rely upon the regulatory methods, and changes in alternate analytical methods will let applicants take advantage of technological changes. This change will eliminate a large number of supplements, particularly with respect to abbreviated applications.

FDA has also closely examined its supplement requirements with respect to containers and closures. FDA agrees with the comment that an applicant should be permitted to change the container and closures within a particular container and closure system, put the change into effect, and notify FDA about the change in the annual report, if the applicant first determines that the approved and proposed container systems have equivalent stability profiles under an accepted protocol (that is, a protocol appearing in the official compendia or one that has received approval in the application, or a supplement to it). The agency is, however, returning to the prior approval category changes in the container size for nonsolid dosage forms because of the potential adverse effects a change in container size may have for liquids and other nonsolid dosage forms. For example, use of a larger container size for a multi-dose parenteral drug may result in an increase in the number of punctures of the vial stopper and, thus, may adversely affect the product's integrity in use over time.

64. Because CGMP regulations require manufacturers to have validated processes, ongoing stability testing programs, detailed written processes, and quality assurance units, comments urged FDA to permit applicants to make changes in packaging components, excipients, dyes, flavors, fragrances, preservatives, and other changes without prior approval if they do not result in changes in product specifications or performance, or product safety and efficacy. Some comments urged that the agency go even further in reducing the burden of supplements by permitting any change in manufacturing or controls without prior approval if it is properly validated using procedures already accepted by FDA.

FDA believes that these comments confuse the different objectives of the CGMP regulations and the drug approval process. The CGMP regulations establish primarily minimum standards for assuring that the drug is not contaminated

during manufacture, and that the drug has the identity and strength and meets the quality and purity characteristics that it purports or is represented to possess. Somewhat differently, the new drug approval process and the supplemental application requirements are intended to ensure that the drug is safe, that its benefits outweigh its risks, and that it is effective. Thus, premarket review is still needed to determine whether a change in packaging components, excipients, dyes, flavors, fragrances, and preservatives will affect the safety and effectiveness of the drug. Indeed, because a color may affect a product's stability, FDA concludes that prior approval of the addition of a color is also needed to assure the safety and effectiveness of the product. With these concerns in mind the agency has revised the final rule to require (as it does now) prior approval of a supplement to add a color.

65. One comment suggested that, under the proposal, prior approval of a supplement would be required to delete claims or indications which may now be made upon submission of a supplemental application and without prior approval. The comment urged FDA to permit applicants to delete, without prior approval, any indication for use or claim for effectiveness considered by the applicant to be unsupportable as a result of the applicant's reconsideration of the data or considered by the applicant to present an unacceptable safety to efficacy ratio.

FDA agrees with the comment and has revised the final rule to continue the current practice of permitting the applicant to remove from labeling false, misleading, or unsupported indications for use or claims for effectiveness at the time a supplement describing the change is submitted.

66. FDA received several comments concerning FDA notification of certain changes in the annual report. The United States Pharmacopeial Convention (USPC) supported FDA's proposal to permit changes in an approved application without requiring a supplement if the changes are made to comply with a change in the compendia. Another comment suggested that the changes that may be described in the next annual report that were listed in the preamble to the proposal should be included in the regulation. One comment suggested that any attempt to list both those changes requiring supplements and those changes not requiring supplements would inevitably leave out some kinds of changes. Several comments suggested that the regulation should clearly identify the container size changes that may be made without a supplement if the applicant informs the agency in the next annual report. Finally, one comment asked that the final rule reflect the preamble statement that applicants would not be required to report changes in information not required in an original application; for example, information about manufacturing practices subject to CGMP regulations.

FDA appreciates the support of the USPC and notes that this change in the agency's supplemental application requirements is based upon close cooperation between FDA and the USPC in the development of compendial standards, including cooperation in the review of data and information supporting changes in standards. FDA has revised the final rule to add to the list of changes that may be described in the annual report. The list includes the following: Any change in the labeling concerning the description of the drug product or in the information about how the drug product is supplied that does not involve a change in the dosage strength or dosage form; an editorial or similar minor change in labeling; the deletion of an ingredient intended only to affect the color of the drug product; an extension of the expiration date based upon full shelf-life data obtained from a protocol approved in the application; a change within the container and closure system for the drug product (for example, a change from one high density polyethylene to another), except a change in size for nonsolid dosage forms, based upon a showing of equivalency to the approved system under a protocol approved in the application or published in an official compendium; the addition or deletion of an alternate analytical method; a change in the size of a container for a solid dosage form, without a change in the container and closure system. FDA emphasizes, however, that the list is not intended to be exhaustive. All changes not falling under one of the two categories requiring supplements are to be described by the applicant in the next annual report to the application. Moreover, any change falling under one of the "supplement" categories that is made simply to comply with an official compendium is also to be described by the applicant in the next annual report. Although FDA believes it is impractical, if not impossible, to describe in the regulations every possible change that could occur in any application, the final rule lists the most significant and common changes that may be made and that are to be described in the annual report. Finally, FDA believes that a list of subjects, like changes under the CGMP regulations for which prior approval has been but is no longer required, would be of only historical interest and could be confusing.

67. One comment suggested that the agency permit applicants to add and update biopharmaceutic information in drug labeling in the annual report and without a supplement.

Drug labeling serves as the standard under which FDA determines whether a product is safe and effective. Substantive changes in labeling, which include changes in biopharmaceutic information, are more likely than other changes to affect the agency's previous conclusions about the safety and effectiveness of the drug. Thus, they are appropriately

approved by FDA in advance, unless they relate to important safety information, like a new contraindication or warning, that should be immediately conveyed to the user.

68. One comment suggested that FDA create a fourth kind of supplement under which an applicant could implement a change 60 days after notifying the agency unless the agency advises otherwise within that time. Another comment suggested 30 days. These supplements might include changes in labeling or revisions to manufacturing or control procedures.

FDA has not adopted this suggestion because of the impact it would have on FDA's priorities. Were such a system instituted, FDA would be forced to rearrange its priorities to ensure that it acted within the required time frame, often with the effect of deferring action on other older and perhaps more important submissions that cannot be implemented without FDA approval. FDA recognizes applicants' concerns about obtaining timely review of supplements, and the agency is addressing this problem by eliminating unnecessary supplements which should, in turn, reduce any backlog. FDA now works closely with applicants who have a special need for timely review of a supplement and, as described above, FDA is establishing a procedure for applicants to request expedited review of certain supplements.

*Procedures for Submission of a Supplement to an Approved Application (§ 314.71)*

69. Noting that a supplemental application can sometimes be as significant as an original application, such as a supplement for a new indication, several comments found beneficial the application to supplements of all procedures and FDA actions on applications under proposed § § 314.100 through 314.170. The comments urged, however, that the agency clearly state that § 314.60 on amendments to unapproved applications, § 314.65 on voluntary withdrawal, and § 314.103 on dispute resolution also apply to supplements.

FDA has revised the final rule to clarify that all procedures applicable to an original application also apply to supplements.

70. One comment suggested that the final rule should specify what actions FDA will take in the event that the agency refuses to approve a supplement for a change that the applicant placed into effect at the time the supplement was submitted. The comment stated that FDA should provide a reasonable time for the applicant to correct the problem, including time to exhaust supplies of the drug or labeling affected by the change, unless a significant safety concern exists.

If FDA refuses to approve a supplement for a change that the applicant has already placed into effect, the agency must consider all the factors surrounding its refusal to approve the supplement, including the applicant's reasons for making the change and the alternatives available to the applicant to resolve the problem. Applicants should be aware that they institute such changes subject to agency approval and that, if circumstances warrant, may be required to discontinue the change immediately. Nonetheless, if circumstances permit, FDA agrees that applicants should be able to correct a problem at minimal expense and without unnecessary waste. Because circumstances can vary greatly, however, FDA is not persuaded that a general statement in the regulations would be appropriate.

*Postmarketing Reporting of Adverse Drug Experiences (§ 314.80)*

71. *Overview.* a. *Comments received.* FDA received a considerable number of comments concerning the proposed reporting of adverse drug experiences of marketed drugs, especially the time frames for such reporting. The current regulations base the reporting times on whether the adverse drug experience is expected or unexpected. All "unexpected" adverse drug experiences are required to be reported within 15 working days, and all "expected" adverse drug experiences are required to be reported in the next periodic report (quarterly in the first year following approval, semiannually in the second year, and annually thereafter). The proposal (with one exception) would have created a standard time frame of 30 working days for reporting almost all kinds of adverse reactions -- serious, nonserious, expected, and unexpected. The one exception was a proposed 15-day alert report for fatal and life-threatening adverse drug experiences not mentioned in the product's approved labeling.

The primary criticism of the proposal made by the comments was that, except for the limited 15-day report, the proposal failed to distinguish the more important adverse drug experiences from the less significant ones. Without such focus, the comments argued, the public health would not be best served because both the agency and the pharmaceutical companies would be spending a disproportionate amount of time processing trivial, known reactions -- time that could be better spent evaluating and following up on serious adverse drug experiences that are more likely to affect the public

health. Comments also complained that, unlike current regulations, the proposal did not make the reporting requirements less frequent for known and nonserious experiences once the drug had been on the market for a period of time.

Given all of these factors, FDA has reevaluated the objectives of the adverse drug reporting system and the regulatory requirements most appropriate to implement them. Based on this review, the agency has modified the final rule in a number of ways designed to increase the system's efficiency and thereby improve public health protection. The details of these modifications are stated below, following a description of the objectives of the reporting system.

b. *Objectives of the reporting system.* Although premarket testing discloses a general safety profile of a new drug's comparatively common adverse effects, the much larger patient population and longer period of use associated with the marketing of a drug provides, for the first time, the opportunity to collect information on rare, latent, and long-term effects, some of which may be serious. Accordingly, the primary objective of the adverse drug experience reporting system is to signal potential serious safety problems with marketed drugs, especially newly marketed drugs. As described below, a signal may be received in a variety of ways. Receipt of the initial signal triggers considerable followup work and analysis before any conclusion about necessary action can be reached (e.g., a "Dear Doctor" letter, revised labeling, or, in rare cases, market withdrawal). Thus, the agency believes that the goal of any regulations in this area should be to direct attention to those reports most likely to contain information on potentially serious safety problems.

c. *The final rule.* The final rule has been modified in the following ways so that the reporting requirements are tailored to signal potentially serious, new information..

(1) *Requirement for 15-day Alert reports.* Under the final rule, all adverse drug experiences that are both "serious and unexpected," and any "significant increase in frequency" of an adverse drug experience that is both "serious and expected," will be required to be reported to FDA as soon as possible, but in any case within 15 working days. These are the adverse drug experiences most likely to reveal serious safety problems that were not revealed during the clinical trials and which, therefore, are likely to necessitate a labeling change or other action to protect the public health. FDA believes that the broadening of the 15-day reporting requirement from that in the proposal, which would have required that only unexpected fatal and life-threatening experiences be reported, will increase public health protection. Throughout the final rule, references to "15-day Alert reports" (unless specified otherwise) refer to reports of "serious and unexpected" adverse drug experiences as well as reports of a "significant increase in frequency" of a serious, expected adverse drug experience.

The final rule defines both "serious" and "unexpected" in order to clarify the 15-day reporting requirement. Both of these definitions have been adopted from a draft guideline that has been made available for public comment (see *48 FR 4049;* January 28, 1983).

For purposes of the final rule, the term "serious" means an adverse drug experience that is life threatening, is permanently disabling, requires in patient hospitalization, or requires prescription drug therapy. In addition, an adverse drug experience that results in death, congenital anomaly, cancer, or overdose is always to be considered serious.

The term "unexpected" means an adverse drug experience that is not listed in the current labeling for the drug and includes an event that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differs from the event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling listed only cerebral vascular accidents. This definition of "unexpected" is based on an evaluation of individual case reports of an adverse drug experience.

The regulation also defines "increased frequency," which is defined to mean an "absolute increase in the number of reports of an adverse drug experience received during a specified time period compared to the number of similar adverse drug experience reports received during an equivalent time period in the past." In contrast to the definition of "unexpected," the definition of "increased frequency" is necessarily based on an analysis of a series of previous adverse drug experience reports, rather than a single report.

The 15-day reporting requirement will apply to any "significant" increase in frequency of a serious, expected adverse drug experience. In order to meet this requirement, applicants are required to review periodically the frequency of reports of "serious" adverse drug experiences that are "expected." The regulation requires applicants to conduct this periodic review at least as often as the periodic reporting cycle, and FDA will provide written notice to applicants when the agency believes that circumstances warrant more frequent periodic review (e.g., approval of a major new indication or where previous reports signal possible safety problems with the drug). FDA will describe in a guideline the factors

which would make an increased frequency "significant" so as to trigger the 15-day reporting requirement, including an increased "rate of occurrence" of the adverse drug experience based on some measure of use of the drug (such as total prescriptions). Given this periodic review and analysis, the final rule requires applicants to report to FDA any significant increase in frequency of a serious, expected adverse drug experience as soon as possible but in any case within 15-working days of determining that a significant increase in frequency exists. Of course, if an applicant receives a large number of reports within a short period of time, so that a significant increase in frequency is readily apparent, a 15-day Alert report would be required at that juncture.

(2) *Format for 15-day Alert reports.* The final rule specifies the format for submission of 15-day Alert reports. This format differs, depending upon whether the report is based on a single "serios and unexpected" adverse drug experience or on a "significant increase in frequency" of a serious, expected adverse drug experience (i.e., a series of events). The final rule requires reports of "serious and unexpected" adverse drug experiences to be submitted on Form FDA-1639 because that form is designed to contain information on individual adverse drug experiences. In contrast, the final rule requires applicants to submit reports of significant increases in frequency in narrative form (including the time period on which the increased frequency is based, the method of analysis, and the interpretation of results) rather than using Form FDA-1639. This is because Form FDA-1639 is not well suited for reporting a group of adverse drug experiences. As stated below, however, the requirement for periodic reports requires that a Form FDA-1639 for each "serious and expected" (as well as "nonserious") adverse drug experience be included in each periodic report. Finally, in order to facilitate expedited processing by the agency, the final rule requires prominent identification of all 15-day Alert reports. .

(3) *Requirement for periodic reports.* For all other adverse drug experiences, the final rule requires periodic reporting at quarterly intervals for the first 3 years following approval, and at annual intervals thereafter. This requirement reflects the agency's experience that the most important safety problems with a new drug are usually discovered during the first 3 years of marketing. Although this periodic reporting requirement is less frequent than the 30-day time frame that was proposed, FDA believes that the quarterly/annual time frame reflects better than did the proposal the relative importance and relative urgency of the information being reported (i.e., known and nonserious adverse drug experiences). Moreover, the final rule is more stringent in this respect than the current regulations, under which quarterly reporting is required for only 1 year before less frequent reporting is permitted.

The final rule also provides that FDA may extend quarterly reporting requirements beyond 3 years (when warranted by adverse drug experience received to date), may reestablish the quarterly reporting requirements at a later point in time (such as following approval of a major supplement), or may require the applicant to submit reports at other specified intervals. Thus, the regulation provides for increased surveillance of drugs when the circumstances so warrant.

The final rule states that quarterly reports are due within 30 days of the close of the quarter (the first quarter beginning on the date of approval of the application) and that annual reports are due within 60 days of the anniversary date of approval of the application. The time frame for submission of annual reports conforms to other annual reporting requirements under § 314.81.

(4) *Format for periodic reports.* The final rule specifies the content of periodic reports. These reports are designed to perform two functions: (a) Report to FDA the adverse drug experiences not previously reported under the 15-day requirement; and (b) present an overview of all the safety-related information learned during that quarter or year. In order to serve this second function, each periodic report is required to contain a narrative summary and analysis of the information contained in the report and an analysis of the 15-day alert reports submitted during the reporting interval; an index of all adverse drug experiences reported for the first time in the periodic report; and a history of actions taken, if any, since the last report because of adverse drug experiences (e.g., labeling changes or studies initiated). FDA believes that this safety profile overview will improve the agency's ability to spot drug safety trends.

(5) *Followup reports.* Several comments addressed the issue of followup reports. These comments urged FDA to require followup reports to be submitted 30 days after the date of receipt of followup information, not 30 days after the date of the original report (as had been proposed). One comment proposed 60 working days for submission of complete followup information on 15-day reports. Another comment asked for clarification about appropriate action if followup information cannot be obtained.

Because FDA has substituted quarterly and annual reports for the proposed 30-day reports, the agency expects that followups will be needed principally for the 15-day alert reports for "serious and unexpected" adverse drug experiences. With respect to these, the final rule requires applicants to investigate them promptly. Along the lines suggested by a comment, FDA has revised the final rule to tie the timing for submission of followup reports to the receipt of new information, rather than to the original report. Thirty working days, however, as suggested by the comment, is too long a

period, given the possible importance of the information. The final rule, therefore, requires the submission of these followup reports within 15 working days of the receipt of new information or as requested by FDA. If the applicant seeks, but cannot obtain, additional information about an experience, a followup report may be required that briefly describes the steps taken to obtain the information and the reason the new information is unobtainable. Any followup information for adverse drug experiences submitted as part of a periodic report may be submitted with the next periodic report.

Finally, like the proposal, the final rule requires that records of adverse drug experiences be retained by applicants for a 10-year period. The record retention requirement has been moved from the "annual reports" section to the "adverse drug experience" section so that all requirements concerning adverse drug experiences can be found in one place in the regulations.

d. *Other options considered.* FDA decided on the time frames described above only after consideration of a wide range of options. For example, several comments urged that fatal and life-threatening adverse drug experiences be reported sooner than 15 working days, such as "immediately," within 24 hours, or within 1 week. One comment argued that FDA should require applicants to submit early reports of all fatal and life-threatening adverse drug experiences, instead of only those that are unexpected. At the other end of the spectrum, several comments urged that reporting intervals should not only become less frequent the longer the drug is on the market, but that at some point in time (e.g., 10 years after approval) reporting of known reactions should be eliminated entirely.

In response to these comments, the agency notes that the final rule does provide for reporting of "serious and unexpected" adverse drug experiences "as soon as possible," with 15 working days being the maximum. FDA strongly encourages the promptest possible reporting of these adverse drug experiences. The agency believes, however, that reducing the time for submitting these reports would serve only to increase considerably the number of incomplete reports received by the agency. A large volume of such reports would make it more difficult for FDA to decide on a course of action, and would tend to clog up the system with useless information. FDA's experience is that 15 working days is sufficient time for applicants to gather enough information to submit a meaningful report, even though some followup may still be required. Moreover, the agency believes that adverse drug experiences already described in a drug's approved labeling need not be reported within 15 days even if those experiences were fatal or life-threatening. The importance of information about such experiences would be limited primarily to the question of whether they occur more frequently than assumed. As discussed above, however, any significant increase in frequency of a serious, expected adverse drug experience is also subject to the 15-day reporting requirement.

With respect to the last comment, FDA has staggered the reporting intervals for known and nonserious adverse drug experiences depending on the length of marketing experience. However, FDA does not believe it would be prudent to eliminate annual reporting across-the-board, even after several years of marketing experience, because of the possibility that long-term or other rare or latent effects might be detected.

72. *Definition of adverse drug experience.* Several comments objected to the scope of the proposed definition of an adverse drug experience, which built certain examples into the definition itself. One comment suggested that the current, more general definition should be retained. Another comment, finding the proposed definition open-ended, urged that the final definition be specifically limited to the listed examples. A third comment suggested that the agency delete information about drug overdose, drug abuse, and drug withdrawal because such information could more efficiently be obtained from the Drug Abuse Warning Network (DAWN) system, sponsored by the National Institute on Drug Abuse. Finally, one comment suggested that the definition should be evaluated to include drug misuse, which would provide useful information for treating emergencies.

FDA disagrees with these comments. FDA believes that the proposed definition of an adverse drug experience, which is retained in the final rule, improves upon the current definition because the specific examples provide clearer notice to applicants of what is required. FDA also believes that the definition should be left open-ended because public health protection requires the reporting of all adverse drug experiences, even those that do not fit into one of the more common categories. With respect to use of the DAWN system, although FDA uses drug abuse information generated by that system, its inherent limitations limit its usefulness such that it should be viewed as complementary to the adverse drug reporting system, with each contributing to an assessment of the abuse liability of drugs. Finally, the agency does not agree that "drug misuse" should be added to the definition because drug misuse often does not result in an adverse event.

73. Several comments objected to including in the definition of an adverse drug experience any failure of a drug product to produce its expected pharmacological action. Because drug products are not expected to be effective in all patients, these comments urged that only significant or unusual failures be reported, a required by current regulations.

FDA agrees that the final rule should be revised so that, as with the current regulation, only a "significant" failure of a drug to produce its expected pharmacological action would be reportable. While most instances of drug failure would be understood by physicians to represent the usual variances of biological responses, some failures of action are more important, reflecting, for example, a drug interaction or an unresponsive patient subpopulation. Such failures may also indicate manufacturing problems or batch failures. It is these types of failure that are likely to appear in the literature or as reports to the applicant, and the final rule requires that they be submitted to FDA.

74. *Tabulation of adverse drug experiences.* Several comments contended that a tabulation in the annual report of adverse drug experience reports already reported on Form FDA-1639 is an unnecessary duplication of the other reporting requirements, and would add greatly to the work of applicants without any obvious benefit. One comment suggested that an applicant's tabulation of adverse drug experiences would be less complete and, thus, less useful than FDA's own data base, from which a tabulation could be made.

FDA has revised this section to require that the applicant provide only an index of all adverse drug experiences submitted for the first time in the periodic report. This index is to consist of a line listing of the applicant's patient identification number and adverse reaction term(s). The index is intended to order the potentially large volume of information being submitted and to provide FDA reviewers with ready access to particular reports when necessary.

75. *Published literature.* Several comments objected to the proposed requirement to transfer information from the published literature onto a Form FDA-1639 and urged, instead, that FDA retain its current rule of simply accepting the published articles themselves. These comments argued that such transfer is an unnecessary clerical exercise that would require major expenditures of time, effort, and money. One comment suggested that even an abstract of the article should be sufficient.

The efficient handling of adverse drug experience reports requires that they be made in a form that is convenient for the agency to process. FDA is currently receiving almost 40,000 adverse drug experience reports annually. To analyze those reports efficiently, the agency has developed a reporting form that reflects FDA's experience in monitoring drug safety in a centralized reporting program. Each item of information on a fully completed Form FDA-1639 (Drug Experience Report) fulfills one of the following four purposes: (1) Recordkeeing information, (2) information necessary to monitor compliance, (3) information relating to the seriousness of the report and the event or reaction, and (4) information relating to the sequential relationship between the drug and the event or reaction. Moreover, as constructed, Form FDA-1639 is also intended to facilitate data entry into FDA's computer base. Given the large number of reports submitted to the agency, and the agency's small staff for reviewing and processing them, FDA's system will work only if applicants transfer reports from the scientific literature to Form FDA-1639's. FDA believes, however, that preparation by the applicant of 1639 forms for literature reports represents a minimal burden because, as described below, the regulations limit the kinds of literature reports that need to be submitted, and because the applicant will necessarily have to review any given literature report to determine if it meets the criteria for reporting. Morever, if the applicant believes that the preparation of a 1639 form represents an undue hardship in any particular instance, the regulations provide that the applicant may arrange with the Division of Drug and Biological Product Experience for an acceptable alternative reporting format.

76. Several comments questioned the need for submitting adverse drug experience reports based on the scientific literature. For example, one comment argued that literature reports often do not contain the information needed to complete FDA's form and, therefore, that this requirement will provide FDA with little useful information. One company estimated that, under the proposed requirement, it would have to copy and submit to FDA almost three 5-drawer filing cabinets of literature articles each year, and that this would amount to over 100 filing cabinets industrywide. According to this comment, the number of additional employees needed by the industry and FDA to copy, submit, and review these articles would also be excessive. Other comments suggested that FDA limit the scope of the published reports falling under this section to, for instance, reports in the published literature "primarily concerned" with the occurrence of adverse drug experiences, or only those relating to fatal or life-threatening experiences. Finally, one comment asked whether the requirement applied to individual experiences reported in letters to a journal.

FDA agrees with those comments that urged FDA, in order to keep the amount of information manageable, to limit the scope of required reports from the scientific literature. FDA has revised the final rule in two ways. First, the final rule limits literature reporting to "serious and unexpected" adverse drug experiences and any "significant increase in frequency" of a serious, expected adverse drug experience (i.e., those subject to the 15-day reporting requirement). By focusing the literature review and reporting on the most important adverse drug experiences, this requirement achieves the objectives of a signaling system while maintaining a reasonable reporting burden on applicants. Reporting of the

vast numbers of individual cases of known or nonserious adverse drug experiences recorded in the literature would not materially advance public health protection.

Second, the final rule limits the kind of literature reports subject to the 15-day requirement in the following ways. With respect to reporting "serious and unexpected" adverse drug experiences, the final rule limits literature reporting to adverse drug experiences appearing in scientific and medical journals as "case reports" or as the result of a formal clinical trial. Case reports are reports of experiences in individual patients, including those appearing in letters to the editor and in studies of adverse effects, but do not include literature reports of adverse drug experiences in clinical trials that do not tie experiences to individual patients. The limitation should help provide FDA with complete, rather than partial and less useful, information about events reported. In addition, limiting the requirement to reports in scientific and medical journals ensures that reports come from scientifically credible sources. As noted above, a Form FDA-1639 is required for each case report, even when a journal may contain less than all items of information needed to complete the form. With respect to reporting a "significant increase in frequency," the final rule limits literature reporting to scientific and medical journals containing reports of either formal clinical trials, or epidemiologic studies or analysis of experience in a monitored series of patients. Once again, this limitation is intended to focus attention on those types of literature reports most likely to yield useful information.

77. Several comments said that the proposal is unclear about when FDA considers an applicant to have knowledge of an experience in a published report. Unsure about when FDA will impute to an applicant knowledge of a published report known by one of the applicant's employees, one comment recommended that applicants be required to report only experiences that employees discover in the normal course of business through a literature review program, or that employees discover on their own time (e.g., while reading a scientific journal at home) and bring to their supervisor's attention at work. However, according to this comment, the regulation should not require that applicants establish literature review programs.

As was clear in both the proposal and the final rule, adverse drug experiences an applicant discovers through an organized literature review program must be reported. Although the final regulations do not require applicants to establish literature review programs, an applicant is obligated to report those experiences that come to its attention in the normal course of business. Whether an employee's knowledge of a report in a scientific journal would be imputed to the applicant will depend upon the factors surrounding the employee's knowledge of the report. As a general rule, however, FDA will consider companies responsible for information known to employees, and companies should adopt procedures that require employees to bring important information to the attention of superiors.

78. Several comments suggested that the regulations should permit a single initial Form FDA-1639 for an adverse drug experience in multiple patients from nonliterature sources because the number of patients is often exaggerated. According to these comments, individual forms could be required for followups of documented patients.

FDA believes that permitting the use of a single initial report for multiple patients with individual forms for followup, while it might reduce by a small number of the forms required, has the potential for creating confusion about the number of experiences reported. It is necessary for FDA, if it is to utilize the data properly, that information on the number of adverse events be received in an unambiguous manner so as to reflect clearly the extent of a problem. The submission of multiple events on a single reporting form is inconsistent with the agency objective. Moreover, a practice of grouping reports on one form would make it harder for FDA to determine whether an experience was covered by an initial report and thus was reported in a timely way, and whether appropriate followup was conducted in each case.

79. *Identification of patients.* Several comments objected to the provision under which FDA would have access to individual patient information. For example, comments suggested that the review of patient records by FDA raises questions about their continued confidentiality. Several comments urged that submission of patient records should require a determination in writing by the Director of the Center for Drugs and Biologics that there is good cause to believe that the reports in the application do not represent actual cases or actual results obtained, or that FDA should provide examples of situations where good cause to review actual reports would exist. Some comments suggested that the proposal did not provide the same types of protection for patient confidentiality accorded by State statutes. These comments suggested that FDA should describe the safeguards the agency will employ to protect and ensure patient privacy.

FDA believes that these comments misunderstood the proposal as it relates to FDA access to patient records. FDA disagrees with the suggestion that its safeguards for information that identifies patients are inadequate. As noted in the proposal, FDA urges applicants not to include names and addresses of individual patients in adverse drug experience reports, although applicants should inlcude some other identifier, such as initials or code numbers. Initials and codes are useful for eliminating duplicate reports of an adverse drug experience. As noted in the regulations, names of patients,

health care practitioners, hospitals, and any geographic identifier are not releasable to the public under FDA's public information regulations in Part 20 (21 CFR Part 20). Moreover, FDA's Division of Drug and Biological Product Experience routinely deletes information that could identify patients, health care professionals, and hospitals before copies of adverse drug experience reports are provided to the public, or even to other components within FDA itself. Thus, FDA believes that the final rule adequately protects confidential information about patients.

80. Several comments also believed that the proposal implied that applicants should maintain in their records the names and addresses of patients. One comment stated that its practice is to retain only identifying information that permits it to find the name and address of a patient, using records maintained by the investigator. Another comment noted that an applicant may be unable to obtain the patient's name, as some hospitals will not release patient identification. The comment suggested that the phrase "upon written request by FDA the applicant shall submit individual patient identification information from designated reports" should be changed to "the applicant shall maintain sufficient patient identification information to permit FDA, by using that information alone or along with records maintained by the investigator of a study, to identify the name and address of individual patients."

FDA agrees with this comment and has revised the final rule to provide that an applicant need only retain identifying information that permits FDA to find the name and address of a patient using records maintained by the applicant or maintained by the investigator in a study.

81. *Postmarketing clinical trials.* Several comments urged that adverse drug experiences from clinical investigations conducted on marketed drugs under an investigational new drug application (IND) should be exempt from the reporting requirements because study blinding will make it impossible to identify whether the adverse drug experience was associated with either the test drug or the control drug. Accordingly, this comment suggested that adverse drug experiences from these studies should be reported to FDA in the final study report. One comment noted that in double-blind studies it is not known whether an experience is associated with a placebo, a control drug, or the study drug, and the code should only be broken for fatal or life-threatening reactions. One comment urged that the regulations clearly specify whether adverse experiences occurring with an approved drug product used in a clinical study under an IND should be reported to the application or the IND. Another comment objected to the use of Form FDA-1639 for reporting experiences from clinical investigations conducted under an IND. According to this comment, those experiences are best reported in the final clinical report, which should be submitted after the study is completed.

FDA agrees with the general thrust of these comments and has revised the final rule to provide that only "serious and unexpected" experiences or a "significant increase in frequency" of a serious, expected experience (i.e., those subject to the 15-day reporting requirement) must be reported when they occur in clinical trials conducted using marketed drugs. As noted above, the 15-day reports are the most important part of the adverse drug experience reporting system, and it is important to keep these reports current. FDA does not interpret this requirement as requiring clinical investigators to break the blinding code, but this requirement does apply to serious, unexpected adverse drug experiences when the code is normally broken anyway (such as when the patient dies or drops out of the study).

82. Several comments also objected to FDA prohibiting the reporting of adverse drug experiences from Phases I and II studies on Form FDA-1639.

The prohibition objected to has been deleted from the final rule. FDA agrees that reporting of "serious and unexpected" adverse drug experiences from clinical trials on marketed drugs required under this section should be submitted on a Form FDA-1639. As noted above, the review of adverse drug experiences by FDA's Division of Drug and Biological Product Experience is geared to this form, and its use also facilitates entry of the information into the computer base for marketed drugs. This interpretation does not apply to 15-day reports of significant increases in frequency which, for reasons described above, are to be reported in narrative form. It should be noted, however, that the final rule does not apply to reporting requirements under the IND regulations (Part 312), where a more detailed type of reporting may be required because much less is known about the safety of unmarketed drugs and, therefore, more extensive information on individual incidents is needed.

83. *Postmarketing surveillance/epidemiological studies.* One comment objected to the submission of adverse drug experience information from postmarketing surveillance/epidemiological studies on Form FDA-1639 in the same fashion as information from spontaneous reports because these studies would generate a large number of reactions that would overwhelm the spontaneous reporting system. The comment suggested that only unexpected adverse drug experiences from those studies be submitted under the schedule for spontaneous reporting, with other experiences summarized and submitted later.

FDA has revised the final rule in response to this comment. First, FDA recognizes that reports occurring in a structured study must be evaluated separately from spontaneous reports. Thus, the agency asks that reports of adverse drug experiences clearly note when an experience occurred in a postmarketing study. The agency will file these study reports separately from spontaneous reports. Second, as with postmarketing clinical trials, the 15-day reporting requirement will apply to these studies only where there is no blinding or when the blinding code is otherwise broken, and these reports are required to be submitted on Form FDA-1639. However, other adverse drug experiences from these studies will be subject to periodic reporting and will be required to be reported following the completion of the study (a study is considered completed 1 year after it is concluded); applicants are encouraged to submit these adverse drug experiences in a format different from Form-1639, if agreed to in advance by the Division of Drug and Biological Product Experience.

84. *Recordkeeping.* Several consumers objected to requiring recordkeeping of adverse drug experience reports for only 10 years, arguing that such data may be useful later if a drug is found to have serious adverse effects that do not show up for many years; for example, if the drug is found to be carcinogenic. In contrast, another comment argued that the requirement that adverse drug experience records be maintained for 10 years is excessive, suggesting instead that complete records be retained for 5 years and a summary of adverse drug experiences be retained for an additional 5 years.

FDA has not found it necessary to rely upon applicant records that are more than 10 years old for evaluating current adverse effects, including delayed effects like carcinogenicity. Thus, the agency cannot now justify a record retention requirement of more than 10 years. In addition, FDA would prefer to be able to obtain full rather than summary records when and if needed. The agency is not persuaded that retaining complete records for 5 years and then reducing them to a summary is less burdensome than simply retaining the records for 10 years. Therefore, the final rule will remain as proposed.

85. *Miscellaneous issues.* On its own initiative, FDA has made several additional modifications to the final rule relating to adverse drug experiences. First, the agency has limited the reporting of adverse experiences from foreign marketing to those considered to be "serious and unexpected" as well as those representing a "significant increase in frequency" of a serious, expected adverse drug experience (i.e., those subject to the 15-day reporting requirement), consistent with other efforts to target FDA resources on the most important adverse experiences.

Second, the final rule, like the current regulations, requires any person (in addition to the applicant) whose name appears on the label of an approved drug product (i.e., a manufacturer, packer, or distributor) to comply with the 15-day reporting provisions on adverse drug experiences. Although FDA proposed to delete this requirement for nonapplicants as part of a broader effort to reduce recordkeeping and reporting requirements generally, FDA believes that the 15-day reporting of adverse drug experiences is sufficiently important, and that it is sufficiently likely that any person whose name is on the approved label will be a recipient of adverse drug experience complaints, that this reporting requirement should be retained. In order to avoid unnecessary duplication of reporting, however, a nonapplicant's obligation under this section may be met by forwarding the adverse drug experience information it receives to the applicant within 3 working days, and by retaining a record of that transmittal.

Third, the agency has continued the current rule of requiring two copies of adverse drug experience reports, rather than the proposal's requirement of only one copy, to expedite review of the reports by the Division of Drug and Biological Product Experience and the Office of Drug Research and Review or the Office of Biologics Research and Review, which both evaluate adverse drug experiences. Because of the large volume of reports received, copying by FDA will unnecessarily delay the review of this important information. The agency believes that spreading this burden among all applicants is both reasonable and efficient. Applicants should send both copies of these reports in the same envelope or package directly to the Division of Drug and Biological Product Experience, and the agency will route the second copy to the Office of Drug Research and Review or the Office of Biologics Research and Review. The final regulation also contains a provision for waiver of the requirement for a second copy (for example, in the quarterly/annual report, the reviewing division may want only the tabular listing of non-15-day reports, rather than full Form FDA-1639's).

Fourth, the final rule contains a caution against the submission of multiple reports for the same adverse drug experience. Thus, an applicant should not include in reports under this section any adverse drug experiences that occurred in clinical trials if they were previously submitted as part of the approved application. If a report applies to a drug for which an applicant holds more than one approved application, the applicant should submit the report to the application that was first approved. If a report refers to more than one drug marketed by an applicant, the applicant should submit the report to the application for the drug listed first in the report.

Finally, FDA has added a provision stating that an adverse drug experience report submitted in accordance with these regulations does not necessarily reflect a conclusion by either the applicant or FDA that the report constitutes an admission that the drug caused or contributed to an adverse effect. This "disclaimer" provision parallels a similar provision recently added to the Medical Device Reporting (MDR) regulation *(49 FR 48272;* December 12, 1984) in response to comments raised concerning products liability consequences of reporting possible adverse effects. FDA advises, however, as it did in the December 12, 1984 notice, that although FDA does not intend for such a report to be viewed as an admission of liability, whether a court will treat a submission to FDA as an admission will depend on factors outside of the agency's control, such as the contents of the report itself.

FDA believes this disclaimer incorporates long-standing agency policy in the drugs area. Both the previous and the new drug regulations require reporting of adverse events, whether or not considered to be caused by the drug in question. FDA is adding the disclaimer provision for purposes of articulating consistency with the new MDR regulation. For the reasons stated in the December 12, 1984 notice, this provision does not require notice and comment rulemaking and will be made effective along with the other adverse drug experience reporting provisions of this final rule.

86. Several comments suggested that FDA combine the adverse drug experience and annual reporting requirements into a single section of the regulation, because the separate sections in the proposal were confusing and duplicative.

FDA believes that separate sections describing the "adverse drug experience reporting" requirements and the "annual reporting" requirements are helpful because both FDA and some applicants have separate organizational components devoted to each of these areas. For example, in FDA, the adverse drug experience reports are evaluated first by the Division of Drug and Biological Product Experience, whereas the annual reports are reviewed by the Office of Drug Research and Review or the Office of Biologics Research and Review.

Nevertheless, FDA agrees that the proposal did not adequately segregate the requirements applicable to adverse drug experience reports from those relating to the more general records and reports, and, therefore, the agency has made the following changes in the final rule: First, the section relating to the "postmarketing reporting of adverse drug experiences" will include all the regulatory requirements relating to this topic, including the provisions relating to the retention of records and the annual tabulation, both of which were located in the "records and reports" section of the proposal. Second, the reporting requirements for adverse drug experiences have been deleted from the "other postmarketing reports" section (called "records and reports" in the proposal) because they are also found in the section in the final rule on adverse drug experience reporting (the proposal had listed them in both sections).

87. One comment suggested that the agency monitor more closely applicants' compliance with reporting requirements and suggested that the proposal was unclear about who is responsible for submitting reports of adverse drug experiences. The comment also asked how the information is made publicly available.

FDA urges health care professionals to submit adverse drug experience reports to FDA on Form FDA-1639. Many professionals submit reports to manufacturers, however, and many manufacturers routinely review the literature on their products. It is the reports obtained by the manufacturer with which these regulations are concerned. The regulations clearly place the responsibility for submitting those reports to FDA on the manufacturer. With respect to public disclosure, § 20.111(c)(3) of FDA's public information regulations governs how this information is made publicly available.

88. One comment stated that FDA's regulatory impact analysis on the proposal did not adequately discuss the impact of the changes in the adverse drug experience reporting system.

This comment was made in conjunction with an objection to the proposed requirement that all adverse drug experiences be submitted within 30 working days, a change which the comment believed was excessive and did not provided a corresponding public health benefit. Because FDA has modified that aspect of the proposal, the corresponding economic concern with respect to the proposed 30-day provision is moot. However, the final regulatory impact analysis does address the economic aspects of the major changes between the current regulations and the final rule.

89. Two comments suggested that over-the-counter drugs that are subject to approved applications and that are not intended for systemic absorption, like antimicrobial mouthwashes or soaps and antidandruff shampoos, should be exempt from frequent reporting of consumer complaints, like rashes or minor skin irritations, particularly if the manufacturer provides a toll free telephone number on labels.

FDA believes that the changes in the final rule -- to require only "serious and unexpected" adverse drug experiences to be reported quickly -- meets the concerns of the comments.

*Other P ostmarketing Reports (§ 314.81)*

90. *NDA -- Field alert report (§ 314.81(b)(1)).* Two comments objected to the proposal specifying that certain reports, required under current regulations to be submitted "immediately," be submitted within 3 working days. These reports covered: (i) Information concerning any incident that causes the drug product or its labeling to be mistaken for, or applied to, another article; and (ii) information concerning any bacteriological contamination, or any significant chemical, physical, or other change or deterioration in the distributed drug product, or any failure of one or more distributed batches of the drug product to meet the specifications established for it in the application. Two other comments, mistakenly believing that the agency intended to require immediate reporting of a broader category of information than currently required, urged that the current language of the requirement be retained because the comments found it preferable to and clearer than the proposed revision. Other comments suggested that FDA allow reports by telephone with written followup information.

Although the agency has retained the proposed wording regarding the kinds of information that are required to be reported under this section, FDA intends the final rule to require the same kinds of reports submitted under the current regulation. The major change from current practice is to require the report within 3 working days. FDA has also revised the final rule to state that this reporting requirement applies only to distributed drug products and that the report should be made to the FDA district office that is responsible for the facility that is the subject of the report. To help the district offices recognize these submissions quickly, these reports have been designated "NDA -- Field alert reports" in the final rule. Because these reports can lead to preventing potential safety hazards from products already in distribution, the agency emphasizes that the reports are required for both confirmed and unconfirmed problems. Telephone reports will be permitted, with prompt written followup.

91. *Annual report (§ 314.81(b)(2)).* Several comments stated that the proposal to require an annual report within 30 days of the anniversary date of approval is unnecessarily burdensome, particularly if adverse drug experiences are reported earlier. One comment suggested a due date of 60 days after the anniversary date, and another comment suggested 6 months. Finally, one comment suggested that annual reports should be eliminated after 3 years of marketing because little new information is obtained after that time.

FDA is persuaded that 30 days may be inadequate for an applicant to compile and prepare an annual report. An annual report under the final rule will differ from current annual reports in that it will contain, in addition to what is currently reported, both a summary of new information about the drug and a description of actions the applicant has taken or proposes to take as a result of that information. Thus, to ensure that the summary is clear, concise, and thoughtful, FDA has revised the final rule to require the submission of an annual report 60 days after the anniversary date of the application.

FDA does not agree, however, that annual reports should be eliminated after 3 years. Animal and clinical data may become available long after a drug is first marketed, and the annual reporting requirement is the most effective means for an applicant to provide it to FDA. Moreover, the annual report is necessary for applicants to inform the agency about changes in the application that are not covered by supplements. Thus, FDA relies upon the annual reporting requirement to monitor continuously the safety and quality of approved drugs while they are marketed.

92. *Summary (§ 314.81(b)(2)(i)).* One comment objected to the requirement for an annual report summary containing a description of the actions an applicant intends to take as a result of new information because, according to this comment, action by an applicant should not wait until the applicant prepares its annual report.

FDA believes that this comment misunderstood the proposal. The final regulations, like the proposal, do not require that an applicant delay action until an annual report is made: instead, the summary is simply required to contain a description of actions the applicant has taken and actions the applicant proposes to take.

93. *Distribution data (§ 314.81(b)(2)(ii)).* One comment objected to what was perceived as a requirement for a single report of units distributed for domestic and foreign use. According to this comment, the requirement would make it difficult for FDA to estimate the incidence of a drug's adverse effects because applicants usually will have much less information about adverse experiences in foreign countries.

FDA has revised the final rule to state clearly that quantities of a drug product distributed for domestic use and quantities distributed for foreign use should be stated separately.

93a. *Chemistry, manufacturing, and controls changes (§ 314.81(b)(2)(iv)).* The final rule retains the current requirement for annual reporting of experiences, investigations, studies, or tests involving chemical or physical properties

of the drug that may affect the drug's safety or effectiveness. This provision was inadvertently omitted from the proposal.

94. *Nonclinical laboratory studies (§ 314.81(b)(2)(v)).* Several comments urged that requirements for reporting nonclinical laboratory studies be limited to active ingredients. One comment asked FDA to require applicants to submit routinely published literature about commonly used drug ingredients, such as acetaminophen, codeine, and atropine, rather than to submit them in annual reports on specific drug products. According to this comment, submission of data on the ingredients rather than on individual products would better enable FDA to monitor the drug products adequately. Another comment urged that summaries of published reports be permitted because the reports themselves often contain lengthy reviews of previous literature. Finally, noting that there is no reason to supply FDA with required information it already has, one comment suggested that FDA limit required submissions to "new" toxicological findings in animal and in vitro studies.

The final rule retains the proposed requirement for reporting nonclinical laboratory studies of inactive ingredients, because both active and inactive ingredients can cause safety problems. FDA has also retained the requirement for submitting study results for inclusion in specific applications rather than making a general submission to the agency. This is because each report an ingredient must be separately evaluated with respect to the drug products that contain it. With respect to published literature, the final rule has been revised to require only summaries of published studies, although the applicant will be required to submit a copy of the published study upon request. FDA has retained in the final rule the requirement for full copies of unpublished nonclinical studies. Finally, the final rule, like the proposal, does limit submissions to "new" toxicological findings in animal and in vitro studies.

95. *Clinical data (§ 314.81(b)(2)(vi)).* One comment objected to the required submission of articles from the scientific literature, rather than simply a bibliography, because the articles are readily available to the agency. Two comments suggested that an applicant should only be required to submit published or unpublished reports that present new and different information that has not been previously submitted, instead of requiring applicants to submit all available reports. One comment suggested a revision of the phrase "review articles, papers, and abstracts in which the drug is used as a research tool," to clarify that papers (as well as abstracts) in which the drugs is used as a research tool should not be reported.

Although FDA has access to the scientific literature, it would impose a significant burden on the agency if its reviewers were required to obtain reprints of literature references. It is properly the responsibility of the applicant to assure that the application is kept current. Since the applicant is expected to monitor the literature for developments relating to its products, it is not, in FDA's opinion, unduly burdensome to require the applicant to copy relevant articles and send them to FDA.

As suggested by two comments, applicants are not required to resubmit information previously submitted. However, the final rule retains the requirement for the submission of information from any new clinical trials (i.e., not previously submitted). Even if such trials do not contain dramatically different information, they often provide new information about, or insights into, the safety or effectiveness of the drug product. Finally, FDA agrees that reports of papers (as well as abstracts) in which the drug is used as a research tool need not be reported, and the agency has revised the final rule to so provide.

96. *Status reports (§ 314.81(b)(2)(vii)).* One comment contended that status reports for postmarketing studies are unnecessary because FDA will be receiving adverse drug experience data on a timely basis.

FDA believes that this comment misunderstood the proposal. All that is required is a "statement of the current status of any postmarketing studies." This is simply a requirement to advise the agency about which postmarketing studies, if any, are ongoing, and what the status of such studies is, such as how close a study is to completion. Detailed reporting of adverse drug experiences is not required under this section.

*Time Frames for Reviewing Applications (§ 314.100)*

97. Several comments objected to establishing limits to the application review time and urged that FDA should emphasize the thoroughness and carefulness of its review instead of merely the speed with which approval decisions are made. One comment suggested that it is unlikely that faster approval could be accomplished without compromising the reliability of FDA's safety and effectiveness decisions. These comments were concerned that the 180-day deadline for reviewing applications may place too much pressure on reviewers and thus reduce the quality of the review. Other comments considered the time frames unrealistic, particularly in view of the proposed changes to increase the number

of communications and meetings with applicants. Another comment suggested that the agency's time frames for action on applications may create unreasonable expectations, given the restrictions on the agency's personnel and budget resources.

This final rule, like the proposal, is intended to establish efficient procedures, including time frames for review, under which the approval process operates, without reducing the high level of public health protection the approval process now provides. The 180-day review period reflects the statutory requirements that apply to the approval process. FDA believes that improvements in the regulations (such as those relating to the format and content of applications), together with managerial improvements, provide a reasonable basis for concluding that the time frames in the final rule can usually be met.

98. One comment suggested that the agency's two 180-day time limits for reviewing and filing applications (which overlap by 60 days) are confusing. The proposal was unclear, according to this comment, about whether an action letter will issue within 180 days of FDA's receipt or within 180 days of FDA's filing of the application. Another comment urged FDA to adopt a single time frame under which the agency would file the application 30 days from the date of its receipt, thus starting the 180-day clock. Finally, one comment suggested that FDA establish a special deadline for action by the Directors of the Office of Drug Research and Review and the Office of Biologics Research and Review on division recommendations on applications.

Although the agency recognizes that there is a potential for confusion, it believes that its separate time frames for reviewing and filing applications are necessary and are not unduly complicated. The agency suggests that reviewers and applicants should focus on the provision for issuance of an action letter (either an approval, approvable, or not approvable letter) within 180 days of FDA's initial receipt of the application. This is the "review clock" (i.e., the period in which the application will be reviewed) and it is not affected by the date of filing. Thus, moving the deadline for filing from 60 days to 30 days would not have the effect anticipated by the comment: The 180-day review period would be already running when either filing date (30 to 60 days) was reached.

The second 180-day period, or "filing clock," plays an important role in only that small number of cases where the applicant chooses to enter the formal evidentiary hearing process following the agency's refusal to approve its application. The reason for the "filing clock" is legal: section 505 of the act requires FDA, within 180 days of "filing," either to approve the application or to issue a notice of opportunity for hearing. The preparation of a notice of opportunity for hearing is far more time consuming than the preparation of a not approvable letter. Therefore, by placing the date of "filing" 60 days into the review cycle, the agency gives itself 60 days at the end of the normal review cycle (i.e., issuance of an action letter) to prepare a notice of opportunity for hearing if one is necessary. (As noted below, this 60 days includes 10 days for the applicant to respond to the action letter, so FDA's time is really 50 days.)

What this means, therefore, is that applicant should rely on the 180-day "review clock" as the measure of review time regarding their applications. As described above, this provision calls for the completion of FDA's review and issuance of an action letter within 180 days of initial receipt of the application. The filing notice after 60 days serves as a status report to the applicant that the application has been found to be sufficiently complete for review purposes, and does not affect the period in which applicants are notified of the approvability of their applications. Except in those rare cases that may culminate in a formal evidentiary hearing, the 180-day "filing clock" has no practical significance.

FDA has retained the proposed provision that the "clocks" may be extended by mutual agreement or by the submission of a major amendment. Any extension applies equally to both the "review clock" and "filing clock." This change is consistent with comments, discussed elsewhere in this preamble, that advocated increased use of advisory committees. These comments recognized that bringing a matter before an advisory committee could raise a need to extend the review period.

*Filing an Application (§ 314.101)*

99. FDA received several comments on the proposed provisions concerning filing an application and procedures to be followed when the agency refuses to file an application. Several comments suggested that the regulations should provide for FDA to file the application within the 60-day period instead of on the 60th day after receipt. Several comments objected, as being insufficient, the 10 days provided in the proposal for an applicant to decide whether to request an informal conference on the agency's refusal to file its application. One comment suggested that the agency allow 30 days for a response, with extensions for good cause. Another comment asked whether an applicant needs to resubmit an

application that it files over protest and suggested that references to "automatic filing" are inconsistent with the requirement that the applicant initiate a conference to file an application over protest.

FDA does not believe a change in the final rule to provide for filing an application in less than 60 days would have any practical effect. As noted above, an earlier filing date would not affect the deadline for issuance of an action letter, which remains 180 days after initial receipt of the application. Moreover, because FDA's time to prepare a notice of opportunity for a hearing (following a not approvable letter, when requested by the applicant) is to be the same as the time for filing the application, an earlier filing would limit the time, which is already short, for the agency to prepare the requisite notice of opportunity for hearing.

In response to comments, FDA has revised the procedures for filing over protest. Under the final rule, when FDA refuses to file an application, the applicant will have 30 days to decide whether to request an informal conference with agency officials (rather than 10 days, as provided in the proposal). The final rule also priovides that such an informal conference must be held before an application may be filed over protest. However, these changes also necessitate modifications of the "review clock" with respect to applications filed over protest, because an informal conference requested on the 30th day following a refusal to file would leave FDA only 90 days (30 days plus the 60 days before filing) in which both to hold the informal conference and complete the review of the application. Under the final rule, an application which the agency refuses to file will be considered received, for purposes of commencing the 180-day review period, on the date the informal conference is requested. This change is needed to ensure that FDA will have enough time to review any application that is subsequently filed over protest. Moreover, dating receipt from the date the applicant requests an informal conference will result in conferences being held promptly because the review period will already have commenced.

In response to one comment, the agency has modified the final rule to provide that an applicant need not resubmit a copy of the application when it is filed over protest.

FDA agrees with the last comment and has removed the reference to automatic filing of an application. Nevertheless, FDA believes that it is clear from the final rule that FDA will file a complete application in 60 days, and that even an incomplete application can be filed over protest (at a somewhat later point) if the applicant insists.

100. One comment suggested that the provision under which FDA can refuse to file an application that is incomplete should include the following phrase "other than case reports and other information not expressly required under this part." According to the comment, this change would clarify that the provisions in the regulations for the routine submission of less than all case report forms does not conflict with section 505(b)(1) of the act *(21 U.S.C. 355*(b)(1)), which requires "full reports of investigations."

FDA believes that the additional wording suggested by the comment is unnecessary. The comment erroneously assumes that only submission of all case report forms satisfies the full reports requirements of the statute. As discussed above, however, case report forms are simply one way in which data from a clinical study can be presented. The final rule requires applicants to submit a combination of summaries, analyses, tabulations, and case report forms, with additional case reports available upon request. These materials satisfy the "full reports" requirements of the act, regardless of whether all case reports are submitted.

101. One comment asked for clarification of the provision under which FDA will refuse to file an application if the drug product that is the subject of the submission is already covered by an approved application. The comment suggested that this should prohibit only an applicant who holds an approved application from filing another application for the same product. The comment stated that the provision should not apply to another applicant filing an application for the drug product.

This provision will permit FDA to refuse to review spurious applications. For example, FDA publishes an "Approved Drug Products List" that identifies applicants who hold approved applications, but this list does not identify distributors. Because some State regulatory officials rely upon the list as an index to legal marketers of drugs, distributors may seek applications for products they already distribute in their own names. FDA's review of such an application would require a commitment of resources, but would not affect the marketing status of the drug under Federal law. Distributors that encounter problems with State procurement or other systems keyed to NDA status should resolve those problems by means that do not involve inappropriate and wasteful use of the NDA process.

*Communications Between FDA and Applicants (§ 314.102)*

102. Several comments agreed with the policies stated in the preamble to the proposal that open communication between FDA and applicants should be fostered and that FDA should promptly communicate with applicants about deficiencies or the need for additional data. These comments, however, urged that these policies be codified in the regulations in order to institutionalize them more formally.

FDA agrees with these comments and, to reflect its commitment to increasing and improving communication between the agency and applicants, has revised the final rule in the following ways. reviewing an application, FDA shall communicate with applicants about scientific, medical, and procedural issues that arise during the review process. Such communication may take the form of telephone conversations, letters, or meetings, whichever is most appropriate to discuss the particular issue at hand. The final rule also requires communications to be appropriately documented, in accordance with § 10.65.

b. The final rule directs FDA reviewers to make every reasonable effort to communicate promptly to applicants easily correctable deficiencies found in an application when those deficiencies are discovered, particularly deficiencies concerning chemistry, manufacturing, and controls issues. The final rule also provides that FDA will inform applicants promptly of its need for more data or information in the application or for technical changes in the application needed to facilitate the agency's review. This policy is designed to permit applicants to correct such readily identified deficiencies relatively early in the review process and to submit an amendment before the review period has elapsed. However, under the final rule, such early communication would not ordinarily apply to major scientific issues, which require consideration of the entire pending application by agency managers as well as the reviewing staff. Instead, these major scientific issues will ordinarily be addressed in an action letter.

c. The final rule contains a new provision for applicants to have an opportunity for an "end-of-review conference" with agency officials. This meeting would be held at the conclusion of FDA's review of an application, as designated by the issuance of an approvable or not approvable letter. The purpose of this type of meeting is to discuss what further steps need to be taken by the applicant before the application can be approved. This meeting will be available on all applications, with priority given to all applications for new chemical entities and major new indications for marketed drugs.

d. The final rule states that FDA will make every effort to grant requests for other meetings that involve important issues and that can be scheduled at mutually convenient times. This policy is designed to facilitate the free exchange of information between FDA and applicants. However, the final rule discourages "drop-in" visits (except for urgent matters, such as to discuss an important new safety issue) in order to minimize disruption of reviewers' work time.

FDA has revised its staff manual guide on communication between FDA and applicants to conform to the provisions of the final rule.

This expanded provision in the final rule embodies FDA's belief that there should be a continuing dialogue between FDA and applicants throughout the IND/NDA process. In the Federal Register of June 9, 1983 *(48 FR 26720)*, FDA proposed revisions to the investigational new drug regulations (IND Rewrite). That proposal encourages all applicants to participate in "end-of-Phase 2" meetings in order to reach an agreement on the overall plan for Phase 3 clinical investigations and the objectives and designs of particular studies. That proposal further encourages applicants to participate in "pre-NDA" meetings in order to ensure that marketing applications present data in a manner suitable for efficient agency review. Moreover, this final rule, as did the proposal, provides for FDA to notify an applicant 60 days after receipt of the application about whether it is acceptable for filing, thus providing early feedback on the application. Finally, the final rule gives applicants a right to an informal meeting approximately 90 days into the review cycle on applications for all new chemical entities and major new indications for marketed drugs. FDA believes that these changes, when seen as a whole, will foster open and timely discussions between reviewers and applicants.

103. FDA also received several comments on the 90-day conference. These comments suggested that FDA extend 90-day conferences to include not only new chemical entities and major new indications, but also all other NDA's and major supplements, such as new dosage forms. In addition, believing the meeting would be held 90 days after filing, which would be 150 days after receipt of the application, one comment suggested that FDA should be prepared to make an intial determination of approvability at the meeting.

FDA has limited the right to a 90-day conference to new chemical entities and major new indications because these are the most complex applications and because the resources needed to extend this right to all drugs are not now available. The agency believes that the provisions described above for presubmission meetings, notice of filing, and early notice of easily correctible deficiencies will in most cases provide adequate feedback to applicants on less complex ap-

plications and supplements. However, as noted above, the agency will entertain requests by applicants for other meetings, and so a 90-day meeting could be requested on applications other than those provided in the final rule.

The agency has revised the final rule to clarify that the 90-day meeting will be held approximately 90 days after the agency receives the application (rather than 90 days after filing) and thus 90 days before the agency would be expected to provide an action letter on it. Because the meeting will be held only midway through the review process, FDA will rarely be able to give its views on the ultimate approvability of the application.

*Dispute Resolution (§ 314.103)*

104. FDA received a number of comments on the issue of dispute resolution. The proposal outlined a new appeals process which the agency implemented at the time of the proposal through a staff manual guide. Several comments suggested that the appeals process is too complex too address minor administrative and procedural disputes which could be resolved more easily and more promptly by an ombudsman. Several comments also felt that the appeals process is inadequate to resolve major scientific and medical policy disputes which, according to these comments, should be referred (as a matter of right) to one of the agency's standing advisory committees.

FDA is committed to resolving disputes with applicants in a prompt, amicable, and equitable way, and it was towards this end that the appeals process referred to above was implemented. In light of these comments, however, together with the agency's newly articulated policy on communication with applicants, FDA has reevaluated the entire issue of dispute resolution and has revised this provision in the final rule in the following ways.

First, FDA agrees with the comments that an ombudsman should be designated to resolve administrative and procedural disputes, and the final rule has been so revised. The role of the ombudsman is to investigate what the facts are and to facilitate a timely and equitable resolution of the issue. Appropriate issues to raise with the ombudsman include resolving difficulties in scheduling meetings, obtaining timely replies to inquiries, and obtaining timely completion of pending reviews. Further details on this procedure are available in a staff manual guide that is publicly available.

Second, upon reevaluation, FDA believes that the recently implemented appeals process is too complex to meet the needs of the NDA review period, and that the same goals can be achieved through alternative means. This conclusion is based in part on the fact that the appeals process was rarely used during its first year, possibly due to the inhibiting effects of the detailed procedure. The appeals process was conceived in response to industry complaints that "stalemates" were often reached with individual reviewers whereby applications could be delayed indefinitely without the involvement of upper lever FDA managers. In addition, applicants appear to perceive FDA as being unreceptive to attempts by applicants to resolve problems informally during the application review process. The new appeals process was designed to meet these concerns by legitimizing access to the system and by requiring automatic review by higher level agency managers. However, FDA believes that other specific provisions of the final rule meet these concerns, and thereby obviate the need for a formal appeals process.

For example, the time frame imposed for review of applications ensures that issues are raised in a timely fashion with upper level managers, including both division directors and the Directors of the Office of Drug Research and Review and the Office of Biologics Research and Review. Moreover, the "ninety-day conference" and "end-of-review conference," described above, provide a timely mechanism for applicants to meet with appropriate agency officials to discuss and resolve, if possible, important issues. For other scientific or medical disputes that arise during the NDA review process, the final rule provides that applicants should first discuss the matter directly with the responsible reviewing officials. If the issue is still unresolved, applicants may request an informal meeting with the appropriate reviewers and supervisors. Ordinarily, such meetings would be held first with the Division Director, then with the Office Director, and finally with the Center Director if the matter is still unresolved. As noted in the provision on communication between FDA and applicants FDA will make every effort to grant requests for meetings that involve important issues and that can be scheduled at mutually convenient times.

FDA recognizes the advantages of utilizing the advice of outside scientific experts in the dispute resolution process, where practical and feasible to do so. The final rule therefore provides that, in requesting a meeting with the agency to resolve a scientific or medical dispute, applicants may suggest that FDA seek the advice of outside experts, in which case FDA may, in its discretion, invite to the meeting one or more of its advisory committee members or other agency consultants, as designated by the agency. The applicant is also free to bring its own consultants. The final rule also provides that, for major scientific and medical policy issues not resolved by informal meetings, FDA may refer the matter to one of its standing advisory committees for its consideration and recommendations. Although this section does not

provide the "right" to advisory committee review requested by some comments, FDA does intend to integrate outside experts more fully into the drug approval process. FDA believes that providing applicants a right to advisory committee review for any disputed issue is impractical from the standpoint of the potential number of controversial issues and the relatively infrequent number of advisory committee meetings. Moreover, utilization of outside advisory committees is committed to the discretion of the agency, and not properly delegated to members of the public. Nonetheless, by involving individual advisory committee members or consultants in the dispute resolution process on a more informal basis, FDA believes that the goal of interacting with the scientific community can be achieved without the delays, resources, and scheduling problems associated with full advisory committee involvements. The role of outside experts in the drug approval process is discussed more fully in the next section of this preamble.

In sum, the dispute resolution procedures in the final rule center on utilizing the most appropriate mechanisms -- be it the ombudsman, informal meetings with outside input, or referral to full advisory committees -- to suit the needs of the particular matter under discussion. Thus, the final rule presents a more comprehensive approach to dispute resolution than did the proposal, and FDA believes these procedures will be useful in addressing the full range of issues that arise during the NDA review process.

In the Federal Register of October 19, 1982 *(47 FR 46622, 46634),* FDA announced that the appeals process would be implemented 30 days after publication, as detailed in a Staff Manual Guide (CDB 4820.5). That Staff Manual Guide extended the applicability of the new appeals process to the IND phase as well. However, in light of the factors discussed above, FDA is reevaluating the utility of that process in the IND phase also. The agency will announce the results of this reevaluation in the IND Rewrite final rule. In the interim, Staff Manual Guide CDB 4820.5 is suspended, pending that reevaluation, and sponsors should utilize the procedures set forth in § 314.103 of this final rule for disputes regarding IND's as well.

*Role of Outside Experts*

105. FDA received several comments relating to the role of outside experts in the new drug approval process. Several comments expressed disappointment that the proposal did not formally establish a role for outside experts in the routine review of applications. These comments, believing that involving outside experts would add to the credibility and quality of the decisionmaking process, urged that applicants be given a "right" to advisory committee review of any marketing application.

FDA agrees that the utilization of outside experts adds to the quality and credibility of the decisionmaking process, and FDA intends to improve utilization of experts from the scientific community during the new drug approval process. For example, FDA has centralized oversight of its human prescription drug advisory committees by establishing a separate office for this purpose within the Office of the Center Director of the Center for Drugs and Biologics. The agency has also begun, on a more regular basis, to include individual advisory committee members in meetings with applicants to discuss scientific issues. The advisory committee issue was not addressed in the proposal because current regulations were seen as providing the necessary flexibility to accomplish these goals. However, in order to respond to comments, this preamble sets forth FDA's policy in this area.

FDA solicits advice from outside experts who serve as either members of advisory committees or as individual consultants. Fifteen standing public advisory committees provide FDA with advice on human prescription drugs. The committees correspond to the drug review groups in the six new drug evaluation divisions, and operate under charters subject to renewal (or cancellation) every 2 years, as required by the Federal Advisory Committee Act.

These advisory committees are also subject to FDA regulations (21 CFR 14.160-14.174), which provide for the committees to advise the Commissioner "generally" on the safety and effectiveness and regulatory control of human prescription drugs, and "specifically" on any particular matter before the agency, including whether the available information is adequate to support a determination that a particular drug meets the statutory standards for proof of safety and effectiveness necessary for marketing approval. High priority items include drugs subject to active IND's and pending NDA's that offer potential therapeutic advances, that pose significant safety hazards, that present narrow benefit/risk considerations, that have novel delivery systems or formulations, that are the subject of a major scientific or public controversy, or that are the subject of special regulatory requirements, such as a limitation on clinical trials, a patient followup requirement, postmarketing studies, or boxed warnings. In addition, applicants can ask to have any relevant matter brought before a full committee.

Advisory committees are used to bring outside experts into the new drug evaluation process in order to: (1) Supplement FDA's in-house expertise; and (2) help agency staff maintain familiarity with current state-of-the-art technology by fostering a close working relationship between FDA scientists and outside experts actively involved in the field. Advisory committee meetings also serve an important function by providing a public forum for discussion of issues.

Advisory committees review, at FDA request, certain critical studies or critical elements of studies on drug products under consideration and labeling issues. They respond to specific questions posed by the agency to identify the adequate and well-controlled studies which demonstrate effectiveness, the seriousness of certain adverse effects, and whether additional studies or data are necessary before a decision can be reached.

FDA also seeks outside advice on clinical research issues. For example, FDA developed approximately 25 clinical guidelines with the help of its advisory committees and others, including the American Academy of Pediatrics' Committee on Drugs and consultants to the Pharmaceutical Manufacturers Association. The guidelines contain generally accepted principles for reaching valid conclusions about the safety and effectiveness of drugs, and they contain views of recognized experts about appropriate methods for studying specific classes of drugs.

Individual advisory committee members have also become involved in the IND process by attending the "end-of-Phase 2" conference, where they aid in the planning of Phase 3 studies. This involvement is explicitly recognized in the IND Rewrite proposal *(48 FR 26732).*

In addition to advisory committee members, FDA also employs representatives from the scientific community as special consultants or expert reviewers. These persons are called upon for advice on technical matters on an ad hoc basis, or are asked to undertake special review assignments in areas where the agency staff may lack particular expertise or available resources. These consultants may also be present at advisory committee meetings.

In summary, FDA believes that the primary goal of the advisory committee (and outside consultant) system should be to help the agency make sound decisions based upon the reasoned application of good science, and the IND/NDA Rewrites reflect this goal. As noted earlier, the IND proposal provides for the inclusion of outside experts in "end-of-Phase 2" conferences during which the design of the major Phase 3 studies is planned. In addition, as described in the preceding section of this preamble, this final rule envisions the participation of outside experts in informal meetings to resolve scientific and medical disputes, and provides for the referral by FDA, if necessary, of major disputes to a full advisory committee.

The principal and perhaps only issue on which the agency disagrees with the comments is whether applicants should be permitted to utilize advisory committees on demand to review applications or resolve scientific disputes. FDA believes that only the agency is in a position to decide the relative importance of which issues advisory committees should consider. Whether to refer a particular marketing application or scientific dispute to an advisory committee is partly a resource issue given the limitations on time and scheduling that restrict the use of advisory committees, and partly a matter of judgment, based on whether FDA decides that the committee is needed to supplement the agency's internal expertise in evaluating the type of data under review. FDA believes strongly, however, that areas of legitimate scientific debate greatly benefit from the broader views that can be provided by an outside advisory committee, and that committee participation significantly enhances the scientific credibility of any decisions reached. Accordingly, FDA intends to make full use of its advisory committees to ensure that this result is achieved. As noted above, it is agency policy to include, as a priority for advisory committee review, marketing applications where the approval decision is a "close call," from either a safety or efficacy standpoint. This policy, together with an applicant's ability to request advisory committee review under § 14.172, should provide applicants adequate access to advisory committees while still allowing the agency to set reasonable priorities.

106. A number of comments addrressed the subject of conflict of interest. Several comments believed that current conflict-of-interest barriers prevent FDA from using many qualified outside experts and recommended that (1) FDA issue clear guidelines to resolve conflict-of-interest problems; (2) the Commissioner waive conflict of interest rules more often where a closer examination of the facts would show that the expert will be able to serve in an unbiased manner; and (3) FDA solicit a less restrictive interpretation of Federal conflict-of-interest statutes and regulations from the Department of Justice. Other comments expressed concern about FDA'a outside experts and asked for assurance that such advisors will be free of conflicts of interest.

FDA's procedures for employing outside experts appear in staff manual guides and in materials provided to outside experts who are employed to advise the agency. These procedures are designed to ensure that advisors' private interests do not conflict with their public responsibilities. Thus, FDA's guidelines with respect to conflict-of-interest issues are

quite clear and widely disseminated. Where highly qualified persons are not free from nongovernmental or private financial interests that present a conflict or potential conflict, FDA may appoint those individuals to serve on a particular committee but exclude them from participation in certain specific matters in which a real or potential conflict of interest exists. In addition, the Commissioner may waive FDA's conflict-of-interest rules in those instances where FDA is persuaded that an outside expert can, despite a conflict of interest, make an impartial and essential contribution to FDA's mission and strict application of the rules would frustrate the best interests of the public. Because of the high level of interest on this issue, however, FDA is reviewing its conflict-of-interest rules to ensure that a proper balance is struck between obtaining advice from those experts most knowledgeable in the field and ensuring that such advice is free from potential bias.

*Approval of an Application (§ 314.105)*

107. FDA received several comments concerning the proposed policy, stated in the preamble, that the agency would approve an application based on draft labeling if the only deficiencies found in the labeling were editorial or otherwise minor in nature. Two comments suggested that FDA codify this policy in the final rule. Another comment suggested that FDA should not approve an application on the basis of draft labeling, because of the importance of labeling during the introduction of a product into the market and the possibility that final printed labeling would not conform exactly to the approved draft labeling. One comment asked how the agency intends to determine whether appropriate changes have been made in final printed labeling after the agency has approved an application on the condition that deficiencies in draft labeling are corrected before marketing.

FDA has concluded that it should approve an application before submission of final labeling if the agency determines that only editorial or similar minor deficiencies exist in the draft labeling, and the final rule has been so revised. This change in practice should expedite drug approvals without compromising the safety or efficacy of drugs. As described elsewhere in this preamble, when FDA anticipates approving an application based on draft labeling, the agency will request a final safety update report under § 314.50(d)(5)(vii)(*b*) to ensure that the approval is based on the most up-to-date safety information available. When an application is approved under this provision, the approval letter will detail the specific changes required in the labeling and state that approval of the application is conditioned upon incorporating those changes exactly as directed. The approval letter will also require applicants to submit to FDA a copy of the final printed labeling prior to marketing. Although applicants will not have to wait for prior approval of the final printed labeling, this procedure will enable FDA to ensure that the final labeling conforms to the conditions of the approval.

108. One comment urged that FDA revise the final rule to state that approval of an application not be dependent upon the availability of the summary basis of approval.

FDA disagrees with this comment. An SBA is prepared for all original applications and supplemental applications for a new use or a substantially different dosage. The SBA is prepared by the supervisory medical officer (group leader) within the reviewing division and becomes part of the final approval recommendation forwarded to the Division Director and the Director of the Office of Research and Review or the Office of Biologics Research and Review. Because FDA supervisors may rely, in part, upon the SBA in determining whether to approve a drug, the agency believes that the SBA needs to be prepared before an application is approved. FDA notes, however, that approval of the application may be based on a draft SBA and precede completion of the final version of that document.

109. One comment, who agreed that FDA must exercise flexibility when applying approval standards to different kinds of drugs, argued that FDA must be even handed when applying the standards within a class of drugs.

FDA agrees generally that applications for similar drugs should be handled in the same manner. Nevertheless, applications for new members of an established class of drugs should take into account experience gained with that class, as FDA will take such information into account in making approval decisions. This may involve, for example, more detailed safety data if marketing experience with the class has revealed special safety concerns.

*Foreign Data (§ 314.106)*

110. FDA received a number of comments on the proposed provision setting forth conditions for approving an application based solely on foreign data. In the past, FDA's policy has been, with rare exceptions, to require some U.S. data (in the form of adequate and well-controlled studies) before approving a new drug for marketing. Nevertheless, while requiring the inclusion of U.S. data in applications, FDA has also relied increasingly upon foreign data in its approval decisions, consistent with the increasing quality and quantity of research performed in other countries. Based

upon this experience with foreign data, the agency, like the medical community in general, has come to recognize the very high quality of drug testing that has emerged from a number of foreign research institutions.

The proposal built on this experience and sought to balance the ability to place increased reliance on foreign data with appropriate safeguard designed to ensure the quality of those data. The proposal removed the "presumption" in current policy that U.S. data would be required and replaced this with the principle that FDA's foremost consideration would be the quality of the data submitted, regardless of the country of origin. Thus, the proposal presupposed that some foreign studies are of comparable quality to U.S. data such that repeating the studies in this country would be neither scientifically necessary nor in the public interest.

At the same time, however, the proposal recognized that foreign data do present three unique problems not associated with domestic data. These involve (1) medical, genetic, and cultural differences between countries; (2) lack of FDA's familiarity with many foreign clinical investigators and facilities; and (3) FDA's inability to conduct on-site verification of many foreign studies. To meet these concerns, the proposal specified that three criteria must be met before the agency could approve a new drug based solely on foreign data. These three criteria were (1) that the foreign data were applicable to the U.S. population and U.S. medical practice; (2) that the studies had been performed by clinical investigators of recognized competence; and (3) that the data could be considered valid without the need for an on-site inspection by FDA or, if FDA considered such an inspection to be necessary, that FDA would be able to validate the data through on-site inspection or other appropriate means.

Thus, the proposal was cast so as to convey both a more open attitude on the part of FDA to consider the merits of foreign data in their own right, but also to safeguard the public health by imposing rigorous criteria that must be met before approval based on those data could be granted. In this way, the proposal sought to focus attention on the scientific merit of the data rather than on unnecessarily rigid rules regarding domestic data requirements.

111. The major concern raised by comments was the possibility that FDA's proposed policy could result in lower quality drugs being approved based on foreign studies. For example, one comment suggested that foreign studies may not meet U.S. standards because foreign research is less concerned with peer review and institutional review boards, features less vigorous controls and lower reporting of adverse drug experiences, and, unlike studies in this country, is not publicly reviewed in the current U.S. medical literature. Several comments believed that the policy should be drafted more narrowly so as to apply only to major medical breakthroughs. Opponents of the foreign data policy also cited the recommendation of the Commission on the Federal Drug Approval Process that suggested that some U.S. clincial experience be required before approving a new drug in this country.

FDA has reviewed these comments in detail, but has concluded that the arguments raised do not warrant any change in the proposed regulation. The essence of the comments was a concern that the three safeguards would be insufficient to ensure the quality of drugs approved solely on the basis of foreign data. FDA does not believe that this concern is valid. The criteria contained in the regulation are rigorous, and the agency intends to apply them with the utmost regard for the public health. The rationale for these criteria is discussed at length in the preamble to the proposed regulation *(47 FR 46643-46644;* October 19, 1982). The agency believes that if the foreign data are applicable to the U.S. population and U.S. medical practice, if the studies are performed by recognized, competent investigators, and if there are no concerns over the validity of the data, then there is no justifiable public health reason not to approve the drug on the basis of the data. In this regard, the agency notes that comments did not suggest inclusion of additional safeguards that, in their minds, would ensure the quality of a drug based solely on foreign data.

As noted in the preamble to the proposed regulations, the agency does agree with comments that the nature of the drug should be taken into account in applying this policy, and that drugs representing major medical breakthroughs would be among those at the upper end of the spectrum. Other drugs falling into this category would be those for diseases that are uncommon in the United States (e.g., tropical diseases and orphan drugs), and drugs on which decision-making is less difficult from a risk-benefit point of view (e.g., topical products). However, the agency does not believe that the policy should be applied exclusively to these types of drugs; rather, any drug meeting the criteria should be included.

Finally, FDA does not agree with the recommendation of the Commission on the Federal Drug Approval Process that at least some U.S. experience with a drug be required before it is approved for marketing in this country. Under the Commission's recommendation, such U.S. experience could be in the form of uncontrolled trials where clinicians administer the drug to patients in settings closely resembling normal clinical practice. The agency believes that the Commission's emphasis on uncontrolled trials in this context is misplaced. First, as described above, FDA believes that the three criteria in the regulation adequately ensure the safety and effectiveness of new drugs prior to marketing and that,

in those situations, uncontrolled trials would not add significantly to the body of data supporting approval. Second, when the regulation's criteria are not met, FDA does not believe that the mere inclusion of U.S. experience in the form of an uncontrolled trial would be sufficient to meet the test for marketing approval. (See *47 FR 46644.)*

112. Several comments supported FDA's proposal to accept foreign data as the sole basis for approval of an application because it recognizes the international nature of clinical research and brings FDA into line with other countries that accept data based exclusively on scientific merit. Some comments, however, suggested that because FDA has inadequate resources and funding to monitor the validity of foreign research and to make on-site inspections, FDA should require more extensive documentation of foreign studies than of domestic studies, including the submission of all case report forms from each foreign study.

FDA agrees that foreign studies forming the sole basis for approval may require more extensive documentation than domestic studies, but the agency believes that the regulations are already flexible enough to accommodate this need. As discussed elsewhere in this preamble, the provisions for submission of summaries, analyses, data tabulations, and certain case report forms should be adequate for FDA's initial review of foreign clinical studies, and FDA will have additional access to data and information, including case report forms, if these are needed. In addition, as noted above, FDA may request full case reports from the most critical studies, and this would include foreign studies as well.

113. Several comments argued generally that the proposed policy was too restrictive. The only specific comments on this point concerned FDA's intention to consider the international reputation, publication experience, participation in meetings, and other factors relating to the competence of foreign investigators. One comment found these tests to be inappropriate, arguing that they are not applied to domestic investigators. Another comment that agreed with the standards urged that FDA establish a mechanism for collecting biographical information to assess the competence of foreign investigators so that individual applicants did not have to.

As noted above, FDA believes that the regulation's three criteria, including the requirement for the clinical investigators to be of recognized competence, are necessary to safeguard the safety and effectiveness of any drugs so approved. Although the review of clinical investigators' competence is highlighted in the foreign data policy, that review is not unique to foreign studies. FDA reviews the qualifications of all clinical investigators, but such a review is more easily conducted with respect to domestic investigators because FDA is generally familiar with them and their institutions. Indeed, FDA has refused to rely on data compiled by domestic investigators who are found to be unreliable. A review of the competence of foreign investigators is therefore also necessary, and FDA believes it appropriate to require the applicant to submit the necessary documentation. FDA believes that this approach will be more practical and efficient than relying on an FDA-compiled biographical library of foreign clinical investigators, which may be incomplete, out-of-date, or otherwise insufficient.

114. Two comments objected to the foreign data policy because it may encourage applicants to conduct more testing abroad. According to these comments, such "export of testing" would have adverse consequences for the United States both economically and scientifically.

Although FDA recognizes there is some merit in the concerns raised by these comments, the agency does not believe it justifiable to impose domestic testing requirements solely for trade restriction purposes, particularly when such requirements might produce an adverse effect on the public health through the delay of approval of new drugs. Moreover, FDA believes that there are two factors mitigating against the concerns raised by these comments. First, in the IND Rewrite, the agency has proposed to give sponsors greater freedom to conduct the early phases of clinical research, in part due to complaints that U.S. regulatory requirements are too strict and are causing U.S. companies to conduct more and more research abroad. Thus, the purported incentive for moving research abroad is being addressed. Second, as discussed in the preamble to the NDA Rewrite proposal, the agency believes that even with the new foreign data policy, most applications will continue to contain some U.S. data. This is due, in part, to the high quality of U.S. clinical investigators as well as to the view that having some domestic physicians familiar with a new drug once it is approved enhances its prospects in the marketplace.

115.-116. One comment asked that FDA hold a presubmission meeting at which an applicant can present to FDA its proposal to rely upon foreign data. Another comment suggested that the agency's appeals process should be available to applicants if FDA refuses to accept foreign data, and that FDA should raise issues regarding the quality or acceptability of foreign data before the relevant standing advisory committee.

The final regulation, like the proposal, specifically encourages applicants to meet with the agency to discuss their plans to submit applications that rely solely upon foreign data. It should be understood, however, that the adequacy of